MOUNT SINAI SCHOOL OF MEDICINE

**Michele La Merrill, PhD MPH**
Environmental Pediatric Fellow
Department of Preventive Medicine

One Gustave L. Levy Pl.,
Box 1057
New York, NY 10029
Tel: 212-824-7003
Fax: 212-996-0407

NTP Workshop: Role of Environmental Chemicals in the Development of Diabetes and Obesity
January 11-13, 2011

January 11th 2011 Public Comment

There is evidence that early life exposure to chemicals increases risk of obesity.
The prenatal and early postnatal periods appear to be critical windows of sensitivity.
Puberty may also be a critical window of sensitivity.

Early life exposures to chemical classes containing PPARγ agonists are associated with obesity.
These chemicals include:

- Bisphenol A (BPA)
- Englitazone
- Monoethylphthalate (MEP)
- Perfluorooctanoic acid (PFOA)
- Pioglitazone
- Rosiglitazone
- Tributyl Tin (TBT)

Early life exposures to polyhalogenated hydrocarbons are associated with obesity.
These chemicals include:

- Dichlorodiphenyldichloroethylene (DDT)
- Dichlorodiphenyltrichloroethylene (DDE)
- Dioxin-like polychlorinated biphenyls (DL-PCBs)
- Hexachlorocyclohexane (HCB)

Evidence suggests that early life exposures to chemicals that increase risk of obesity appear to operate in a non-linear dose-response manner. Cachexia often occurs at high doses whereas body and/or adipose mass gain occurs at low doses of the same chemical.

Research findings indicate there may be gender specific effects of early life chemical exposures that increase risk of obesity.

Sincerely,

[Redacted]

Michele La Merrill, PhD MPH

# Childhood Obesity and Environmental Chemicals

Michele La Merrill, PhD, MPH,[1] and Linda S. Birnbaum, PhD, DABT[2]

[1]Mount Sinai School of Medicine, New York, NY
[2]National Cancer Institute, National Institute of Environmental Health Sciences, Research Triangle Park, NC

## OUTLINE



## ABSTRACT

Childhood and adolescent rates of obesity and overweight are continuing to increase in much of the world. Risk factors such as diet composition, excess caloric intake, decreased exercise, genetics, and the built environment are active areas of etiologic research. The obesogen hypothesis, which postulates that prenatal and perinatal chemical exposure can contribute to risk of childhood and adolescent obesity, remains relatively underexamined. This review surveys numerous classes of chemicals for which this hypothesis has been explored. We focus on human data where they exist and also discuss the findings of rodent and cell culture studies. Organochlorine chemicals as well as several classes of chemicals that are peroxisome proliferator-activated receptor agonists are identified as possible risk factors for obesity. Recommendations for future epidemiologic and experimental research on the chemical origins of obesity are also given. ***Mt Sinai J Med 78:22–48, 2011.*** © *2011 Mount Sinai School of Medicine*

**Key Words:** environmental exposure, growth and development, obesity.

**Address Correspondence to:**

**Michele La Merrill**
Mount Sinai School of Medicine
New York, NY
Email: Michele.LaMerrill@mssm.edu

The number of children who are obese and overweight continues to rise in most countries across the world.[1] In the United States (US), the prevalence of obesity and overweight is growing rapidly among children and adolescents.[2,3] For instance, West Virginia is among the states with highest adult obesity prevalence, and in a West Virginian adolescent medicine clinic, 37% of adolescents had an age- and gender-adjusted body mass index (BMI; body weight in kg divided by height in meters squared) greater than the National Health and Nutrition Examination (NHANES) III 95th percentile.[3] Rising obesity prevalence is a concern for many reasons. The risk of life-threatening diseases, such as diabetes, cardiovascular disease, and cancer, is increased in obese persons.[4–6] Further, obesity has overtaken cigarette smoking as the most costly and detrimental preventive cause of terminal diseases in the US, with latest estimates suggesting that obesity accounts for 17% of all US medical costs each year.[7]

Although the increasing prevalence of obesity is usually attributed to changes in diet, physical activity, and underlying genetic susceptibility, the possibility that environmental chemicals could influence obesity is relatively underexplored. Early life exposure to environmental chemicals is beginning to be examined as a contributing cause of the obesity epidemic due to the potentially critical role of prenatal and perinatal metabolic programming in later risk of obesity. Thus, we find it may be useful to think about obesity not just in terms of genetics and lifestyle, but also in terms of how early life exposure to these "obesogenic"

Published online in Wiley Online Library (wileyonlinelibrary.com).
DOI:10.1002/msj.20229

chemicals might be setting the stage for weight gain later in life. In this review, we first discuss metabolic programming and the unique physiology of obese children and adolescents. We next examine the evidence of associations between chemicals and obesity, with an emphasis on human research results where they exist. There are numerous recent reviews focused on experimental evidence of the mechanisms of obesity caused by chemicals, and the interested reader is referred to these publications.[8,9] This review concludes with a discussion of the strengths and weaknesses of obesogen research as well as recommendations on future directions of obesogen epidemiological and experimental research. Although obesity is closely associated with metabolic syndrome and diabetes, these topics are outside the scope of this review.

## UNIQUE SUSCEPTIBILITY OF OBESE CHILDREN AND ADOLESCENTS

### Prenatal and Perinatal Metabolic Programming

Metabolic programming during prenatal and perinatal development has become an active area of obesity etiology research that is rife with seeming contradictions. Caloric restriction during pregnancy at the time of the Dutch famine during World War II is associated with a greater occurrence of obesity in adult offspring.[10] In contrast to a nutritionally limited environment, higher maternal prepregnancy BMI and higher gestational weight gain are associated with increased birth weight and fat mass at birth, and increased BMI in young and adult offspring.[11,12] Similarly, dietary fat–induced paternal obesity also is also associated with a disruption in insulin secretion and glucose tolerance in offspring.[13] Maternal diabetes is also associated with increased birth weight as well as childhood overweight and obesity.[14,15] Paradoxically, children and adults born small for gestational age also have an increased risk of obesity, which may be mediated by rapid compensatory postnatal growth.[16,17] Even studies in which adiposity outcomes are only measured in children capture adult risk because prepubertal BMI correlates to BMI in young adults, and BMI in young adults predicts BMI in mature adults.[18]

Related to the field of metabolic programming are the concepts of the developmental origins of human adult disease (DOHAD) and windows of susceptibility to toxicants.[19,20] Research in animals and humans shows that the developmental processes that occur at embryonic, fetal, and infantile stages are especially vulnerable to disruption from relatively low doses of certain chemicals (Figure 1). When organs and tissues are developing, they are particularly at risk to toxic insult.[20] This was first observed decades ago in the case of lead and other metals that could harm neurological development as a result of *in utero* and childhood exposures. This concept also applies to agents that alter metabolic homeostasis during development, which can lead to obesity, diabetes, and metabolic syndrome.[19,21–24] In particular, exposure to toxicants during the organogenesis of tissues involved in metabolic homeostasis (eg, adipose, liver, skeletal muscle, pancreas, and brain) may play an important pathophysiological role in the development of childhood obesity (Figure 1). Whereas much of organogenesis occurs prenatally, adipose, skeletal muscle, pancreas, and brain continue to develop postnatally.[19] It remains possible that fetal adaptations to toxic metabolic insults restrict the scope of adaptive responses to a toxic postnatal environment. If this were the case, one could envision DOHAD similar to the multistage carcinogenesis hypothesis, where risk of obesity results from multiple toxic insults that temporally span the various stages in which metabolic tissues are developing.

*Whereas much of organogenesis occurs prenatally, adipose, skeletal muscle, pancreas, and brain continue to develop postnatally.*

### Unique Physiology of Obesity

There are many reasons why children are not merely small adults in terms of the ways that their environment affects them. Similarly, the physiology of obese persons is not the same as the physiology of lean persons. Thus, it follows that obese children have unique physiology. In obese children, glucose and lipid metabolism tend to be dysfunctional, as evidenced by the prevalent comorbidites of insulin resistance, hyperlipidemia, and metabolic syndrome.[25] Obesity is a chronic inflammatory state, which likely explains part of the increased incidence of asthma in obese children.[25,26] The endocrine system also functions differently in obese persons. For instance, adipocytes produce hormones such as estrogen and leptin, which are produced in excess in obese people. It is not surprising that obesity is associated with decreased reproductive health, and there is no indication that adolescent reproductive health is an exception. The fact that polycystic

DOI:10.1002/MSJ

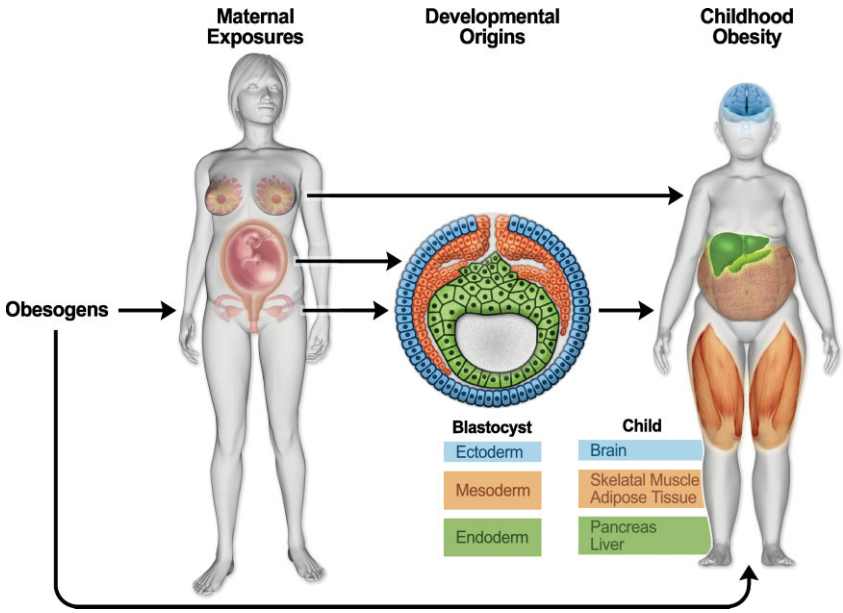


Fig 1. Maternal chemical exposures are associated with childhood obesity. Maternal exposure to chemicals may target offspring through gametes, placenta, or milk. Potential target tissues of obesogens in offspring can arise through all 3 germ cell layers of the blastocyst, which continue to differentiate postnatally.

ovarian syndrome is more common in obese females may in part be due to the altered endocrine state of obesity. Childhood obesity is also associated with entering puberty earlier.[27]

*The physiology of obese persons is not the same as the physiology of lean persons.*

The pharmacokinetic (PK) and pharmacodynamic (PD) properties of environmental chemicals are different in obese children compared with lean children. Human PKPD studies tend to be overly simplified, in part due to the ethical concerns of deliberate human exposures to toxicants. Thus, PKPD studies in obese and/or developing mammals have mostly been explored in rodents.

A given quantity of a lipophilic exposure will be diluted in an obese individual because their total adipose mass is greater than that of their lean peers. Body and adipose tissue weight gain over time furthers the dilution effect to lower serum levels independently of elimination of the chemical.[28] Although all people can gain mass, the temporal dilution of chemicals by mass gain is particularly salient in children because of their rapid growth. Further, the metabolism of chemicals such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and dichlorodiphenyltrichloroethane (DDE) is delayed and half-lives extended in obese mammals relative to lean mammals.[29–31] Perhaps counterintuitively, as TCDD exposure levels decrease, the half-life actually increases.[29] Thus, the chemical concentration in blood may be lower in obese persons due to dilution, but the cumulative exposure may be higher because of the extended half-life (particularly if exposure is relatively low in the case of dioxin-like compounds).

Many candidate obesogens are lipophilic chemicals and are therefore deposited in fat tissues. In the case of TCDD, its distribution into adipose tissue is greater at low exposure levels.[29] Obese persons tend to have higher lipid levels in circulation, and in the case of lipophilic chemicals whose blood concentrations are dependent on blood lipid levels, whole blood chemical quantities may appear higher in obese persons than lean persons even if total body burdens are equivalent.[32,33] In other words, the dilution effect of higher body mass may be masked by higher blood lipids when sampling serum or whole blood to assess lipophilic chemical exposure. In some cases, storage of lipophilic chemicals in fatty tissues appears to sequester the chemicals from their toxicity target tissue, and thus obesity may be protective.[34] However, if the target tissue of toxicity has a high fat content, the lipophilic chemical will be stored where it is most able to cause toxicity. Thus, the notion of protective sequestration of lipophilic chemicals may be irrelevant in the case of obesogens, because

DOI:10.1002/MSJ

metabolic homeostasis is partially regulated by adipose tissue.

*If the target tissue of toxicity has a high fat content, the lipophilic chemical will be stored where it is most able to cause toxicity.*

## CANDIDATE OBESOGENS

### Persistent Organic Pollutants

#### Dioxins and Dioxin-like Compounds

Dioxins are persistent organic pollutants (POPs) that are primarily byproducts of industrial activities. The most potent dioxin is TCDD, a high-affinity ligand of the aryl hydrocarbon receptor (AhR), and as such its toxicity is mostly attributed to AhR binding as well as its persistence. Other AhR ligands include polychlorinated dibenzofurans, and some "dioxin-like" polychlorinated biphenyls (DL-PCBs), which were used extensively in industrial applications. These AhR ligands are frequently analyzed according to toxic equivalents (TEQs), which multiplies the mass of dioxins, DL-PCBs, and furans by a potency factor that ranks their toxicity relative to TCDD.[35] All PCBs that do not bind AhR are called non–dioxin like (NDL).

Most of the prospective studies of developmental exposures to dioxins and PCBs had no association with child, adolescent, or adult obesity (Table 1). For instance, there was no association of either TEQ (calculated from exposure assessment of dioxins and PCBs) or PCB mass in milk on the body weights of toddlers (Table 1).[36] Summed PCBs in maternal and cord plasma samples were associated with a transient decreased change in the standard deviation score (SDS, a descriptive statistic used to describe variability[37,38]) of body weight from birth to 3 months old in formula-fed infants (Table 1).[36] Further, prenatal PCB exposure was not associated with BMI or body mass of adult daughters.[39] Though these 2 studies were fairly small, a larger prospective study of *in utero* exposure to PCBs had a trend of increased association with higher body weights in adolescent girls, yet this was not statistically significant nor was this seen in boys (Table 1).[40]

Only 1 prospective study of developmental PCB exposure found a positive association with adiposity: PCBs in umbilical cord levels of Belgian children were positively associated with BMI SDS between the ages of 1 and 3 years old, which was when the study ended.[41] Although the TEQ was not associated with BMI SDS in this study, the only dioxin-like compound that contributed to the TEQ was PCB118, which has a relatively low contribution to total TEQ.[41]

The majority of the epidemiology evidence in favor of a positive association between PCBs and obesity comes from cross-sectional studies of adults, although a few studies that included children also exist (Table 1).[42,43] Cross-sectional studies of adult PCB exposures have consistently shown a positive association with measures of obesity.[43–46] Further, there are 3 epidemiology studies of adults that found a positive association between dioxins and obesity and only 1 study of adults that did not.[43–46]

Experimental research on dioxins and dioxin-like compounds as obesogens is quite sparse and may be biased by high doses. High doses of a PCB mixture (30 mg/kg body weight/day on gestation day [GD] 10–18) caused a transient decrease in offspring body mass.[47] Elsewhere prenatal and lactational TCDD (single exposure to 1 μg/kg body weight on GD 12) had no effect on adiposity in several mouse strains.[48,49] Perhaps the dose of TCDD and PCBs in these studies was too high to detect obesogenic effects, as TCDD induces adipocyte differentiation at low doses and suppresses it at high doses.[50–52] Adipocyte differentiation is considered to play a role in the etiology of obesity primarily during childhood, as adipocyte numbers are currently thought to be in a steady state in adults, regardless of whether they are lean or obese.[53,54] As was seen with TCDD, low dose of dioxin-like PCB77 also stimulated adipocyte differentiation.[52] Further, recent evidence suggests that peroxisome proliferator activated receptor (PPAR) $\gamma$ expression may be elevated by lower doses of TCDD and DL-PCBs.[52,55] Consistent with these findings, exposure to a PCB mixture (6 mg/kg body weight/day on GD 6–postnatal day [PND] 21) was associated with a transient increase in body weights of offspring on PND 16–20, in a 34-day study.[56] Whereas adult exposure to PCB126 (a DL-PCB) had no impact on body mass in mice in one study,[57] another study found that adult mice exposed to PCBs have AhR-mediated increased body mass as well as adipocyte hypertrophy.[53]

#### Organochlorine Pesticides

Several persistent organochlorine pesticides have been implicated in obesity. Although they have not been in commercial use in the US for >20 years, they are used abroad. Dichlorodiphenyltrichloroethane (DDT) is rapidly metabolized to dichlorodiphenyldichloroethylene (p,p′-DDE), which has a half-life of about 10 years in humans.[31] Thus,

DOI:10.1002/MSJ

DOI:10.1002/MSJ

**Table 1.** *Child and Adolescent Obesity and Organochlorine Exposures Organized by Chemical Class With Ascending Ages per Chemical.*

| Chemical | Age at Exposure (n) | Design | Duration of Follow-Up (Sex) | Exposure | Outcome |
|---|---|---|---|---|---|
| Dioxin-like compounds | | | | | |
| TEQ of PCDDs and DL-PCBs[36] | 2 weeks (105) | Prospective | Term birth–42 months (M/F) | 28.0–155.0 ng TEQ/kg milk fat | NS BW |
| TEQ of PCDDs[43] | 15–73 years (1374) | Cross-sectional | 0 (M/F) | 4.6–11.2 pg TEQ/g whole blood lipid | NS BMI ≥ 25 |
| TEQ of PCDFs[43] | 15–73 years (1374) | Cross-sectional | 0 (M/F) | 2.9–6.8 pg TEQ/g whole blood lipid | NS BMI ≥ 25 |
| TEQ of PCB118[41] | Birth (138) | Prospective | Term birth–3 years (M/F) | 6.0–78.7 pg TEQ/g cord plasma lipid | NS change in BMI SDS* |
| TEQ of DL-PCBs[43] | 15–73 years (1374) | Cross-sectional | 0 (M/F) | 4.4–13.0 pg TEQ/g whole blood lipid | Increased trend of BMI ≥ 25 (OR = 2.6 between Q4 and Q1) |
| PCB118[42] | 14–15 years (887) | Cross-sectional | 0 (M) | 2.8–13.6 ng/g serum lipid | Increased BMI ($\beta^{\dagger} = 0.56$ kg/m$^2$ per doubled exposure) |
| PCB118[42] | 14–15 years (792) | Cross-sectional | 0 (F) | 2.4–11.6 ng/g serum lipid | Increased BMI ($\beta^{\dagger} = 0.74$ kg/m$^2$ per doubled exposure) |
| NDL-PCBs | | | | | |
| PCBs[59‡] | First trimester (518) | Prospective | 14 months (M/F) | 18.2–67.0 ng/g maternal serum lipid[§] | NS rapid growth, NS BMI $z$ score* |
| PCBs[36‡] | Birth (207) | Prospective | Term birth–42 months (M/F) | 0.1–2.1 μg/L cord plasma | Decreased change in BW SDS birth–3 months ($\beta^{\dagger} = -0.4$ change in BW SDS per μg/L) |
| PCBs[41‖] | Birth (138) | Prospective | 1–3 years (M/F) | 9–442 ng/g cord plasma lipid | Increased change in BMI SDS 1–3 years ($\beta^{\dagger} = 0.003$ kg/m$^2$ SDS per ng/g lipid) |
| PCBs[40¶] | Prenatal (594) | Prospective | 14 years (M/F) | 0.5–5.5 ppm transplacenta[#] | NS BW |
| PCBs[39¶] | Prenatal (169) | Prospective | 20–50 years (F) | Quintiles: 0.1, 1.9, 3.5, 7.1 μg/L maternal serum[#] | NS BMI, NS BW |
| PCBs[40¶] | Postnatal (594) | Prospective | 14 years (M/F) | 0.2–23.1 total mg consumed from milk[#] | NS BW |
| PCBs[42**] | 14–15 years (887) | Cross-sectional | 0 (M) | 42.7–141.3 ng/g serum lipid | Decreased BMI ($\beta^{\dagger} = -2.4$ kg/m$^2$ per doubled exposure)[††] |
| PCBs[42**] | 14–15 years (792) | Cross-sectional | 0 (F) | 30.3–98.5 ng/g serum lipid | Decreased BMI ($\beta^{\dagger} = -2.0$ kg/m$^2$ per doubled exposure) |

(*continued overleaf*)

**Table 1.** *(Continued).*

| Chemical | Age at Exposure (n) | Design | Duration of Follow-Up (Sex) | Exposure | Outcome |
|---|---|---|---|---|---|
| Organochlorine pesticides | | | | | |
| DDTs[58] | Prenatal (304) | Prospective | 10.8–20.0 years (M) | 1.8–33.1 μg/g maternal serum lipid | NS BMI, NS tricep skinfold thickness, NS central adiposity |
| DDE[59] | First trimester (518) | Prospective | 14 months (M/F) | Quartiles: 71.7, 116.9, 186.2 ng/g maternal serum lipid | Increased rapid growth 6 months (RR = 2.4 between Q2–4 and Q1), increased BMI *z* score* 14 months (RR = 1.2 per log ng/g lipid) |
| DDE[39] | Prenatal (169) | Prospective | 20–50 years (F) | Quintiles: 1.5, 2.9, 6.1, 9.4 μg/L maternal serum[#] | Increased BMI ($\beta^{\dagger}$ = 2.88 kg/m$^2$ per μg/L between Q2–Q5 and Q1), increased BW ($\beta^{\dagger}$ = 9.22 kg per μg/L between Q2–Q5 and Q1) |
| DDE[40] | Prenatal (315) | Prospective | 14 years (M) | 0.3–23.8 ppm transplacenta[#] | Increased BW 14 years (>4 ppm group mean = 60.6 kg, ≤1 ppm group mean = 53.7 kg) |
| DDE[40] | Prenatal (277) | Prospective | 14 years (F) | 0.3–23.8 ppm transplacenta[#] | NS BW |
| DDE[41] | Birth (138) | Prospective | Term birth–3 years (M/F) | 24–1816 ng/g cord plasma lipid | Increased BMI SDS* 3 years (450 ng/g group mean = 0.1 kg/m$^2$ SDS,* 63.7 ng/g group mean = −0.7 kg/m$^2$ SDS*)[‡‡] |
| DDE[40] | Postnatal (594) | Prospective | 14 years (M/F) | 0.2–96.3 total mg consumed from milk[#] | NS BW |
| DDE[42] | 14–15 years (887) | Cross-sectional | 0 (M) | 46.8–403.9 ng/g serum lipid | NS BMI |
| DDE[42] | 14–15 years (792) | Cross-sectional | 0 (F) | 39.3–247.1 ng/g serum lipid | NS BMI |
| HCB[59] | First trimester (518) | Prospective | 14 months (M/F) | Quartiles: 22.8, 41.0, 66.3 ng/g maternal serum lipid | NS rapid growth, NS BMI *z* score* |
| HCB[60] | Birth (482) | Prospective | Term birth–6.5 years (M/F) | 0.5–1.0 ng HCB/mL cord serum IQR | Increased BW 6.5 years ($\beta^{\dagger}$ = 1.9 kg between Q4 and Q1), increased BMI 6.5 years ($\beta^{\dagger}$ = 1.0 kg/m$^2$ between Q4 and Q1), increased overweight risk (RR = 1.7 per log ng/mL), increased obese risk (RR = 2.0 per log ng/mL) |

(*continued overleaf*)

DOI:10.1002/MSJ

DOI:10.1002/MSJ

**Table 1.** *(Continued).*

| Chemical | Age at Exposure (n) | Design | Duration of Follow-Up (Sex) | Exposure | Outcome |
|---|---|---|---|---|---|
| HCB[42] | 14–15 years (887) | Cross-sectional | 0 (M) | 15.2–34.5 ng/g serum lipid | Decreased BMI ($\beta^{\dagger} = -0.7$ kg/m$^2$ per doubled exposure)[§§] |
| HCB[42] | 14–15 years (792) | Cross-sectional | 0 (F) | 12.3–26.6 ng/g serum lipid | Decreased BMI ($\beta^{\dagger} = -0.6$ kg/m$^2$ per doubled exposure) |
| $\beta$HCH[59] | First trimester (518) | Prospective | 14 months (M/F) | Quartiles: 21.7, 32.2, 47.3 ng/g maternal serum lipid | NS rapid growth 6 months old, NS BMI $z$ score* 14 months old |

**Abbreviations:** BMI, body mass index; BW, body weight; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; DL, dioxin-like; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; IQR, interquartile range; NDL, non–dioxin-like; NS, not significant; OR, odds ratio; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzodioxin; PCDF, polychlorinated dibenzofuran; ppm, parts per million; RR, relative risk; SD, standard deviation; SDS, standard deviation score; TEQ, toxic equivalents; WHR, waist-to-hip ratio.

*Descriptive statistic used to describe variability.[38]

†Change in the outcome (eg, BMI, BW) per 1-unit change in the exposure.

‡PCB118 + PCB138 + PCB153 + PCB180; note PCB118 is a DL-PCB.

§Range of means across subgroups.

PCB118 + PCB138 + PCB153 + PCB170 + PCB180; note PCB118 is a DL-PCB.

¶PCB congeners not reported.

#Extrapolated.

**PCB138 + PCB153 + PCB180.

††Larger change in $\beta$ in children with low exposure (below PCB median) compared with high exposure (above PCB median); above-median and below-median PCB groups are both associated with decreased $\beta$.

‡‡Larger change in BMI SDS in children of smoking mothers compared with nonsmoking mothers.

§§Larger change in $\beta$ in children with low exposure (below HCB median) compared with high exposure (above HCB median); above-median HCB group associated with increased $\beta$ and below-median HCB group associated with decreased $\beta$.

Larger change in $\beta$ in children with low exposure (below median) compared with high exposure (above median); above-median and below-median HCB groups both associated with decreased $\beta$.

the presence of DDT indicates a recent or current exposure and p,p′- DDE tends to imply a long-term body burden. Hexachlorobenzene (HCB) and hexachlorocyclohexane (HCH, often called lindane) also have long half-lives.

Of the 5 prospective studies of maternal exposure to DDE, 4 found a positive association with measures of obesity in offspring (Table 1). A prospective study of 169 women in the Michigan fish-eater cohort (1973–1991) revealed that prenatal DDE exposure was associated with significantly increased the BMI and body mass of adult daughters in a dose-dependent manner.[39] Further, as Belgian umbilical-cord DDE increased, BMI SDS increased in 2- and 3-year-old children; the effect of increasing DDE levels on the BMI SDS was greater in children born to women who ever smoked compared with children of nonsmoking mothers.[41] Transplacental exposure to DDE was associated with increased body weight of adolescent boys; however, this was not seen in girls.[40] This was not seen in a population with higher DDT + DDE exposure levels, where summed DDT and DDE were not significantly associated with the BMI, tricep skinfold thickness, or central adiposity of adolescent boys.[58]

*A prospective study of 169 women in the Michigan fish-eater cohort (1973–1991) revealed that prenatal DDE exposure was associated with significantly increased the BMI and body mass of adult daughters in a dose-dependent manner.*

It was recently reported that the risk of rapid infant growth among infants born of women above the lower quartile of DDE exposure was 2.4× the risk of rapid growth in those born of women in the lowest quartile of DDE exposure (Table 1).[59] As was seen in the studies by Gladen *et al.*, this effect may have been limited to children born of women with moderate DDE exposures because when prenatal DDE exposures exceeded 750 ng/g, no rapidly growing infants were observed.[40,58,59] When the children of this study were 14 months old, the risk of elevated BMI *z* scores (another measure of variability, elevated defined here as ≥1.44) increased 1.40 for each unit increase in log ng DDE/g lipid.[59]

There are far fewer studies of prospective developmental exposures to HCB and HCH (Table 1). For instance, the association between cord-blood HCB levels and childhood obesity was consistent with a positive dose effect of HCB on body weight and BMI when children were 6.5 years old (Table 1).[60] Cord-blood HCB levels >0.46 ng HCB/mL were associated with a 70% increase in the risk of being overweight and doubled the risk of being obese at age 6.5 years.[60]

The only cross-sectional study of children and DDTs found a negative association between DDE and BMI in adolescents of both sexes (Table 1).[42] However, in the majority (5/6) of cross-sectional studies of adults, DDT and/or DDE exposures are associated with increased obesity.[42,44,45,61–63] Similarly, serum HCB was associated with decreased BMI in adolescent boys and girls cross-sectionally.[42] The opposite trend was seen in adults from this same region of Belgium, where serum HCB levels in adult men and women were associated with increased BMI after adjustment for other environmental exposures.[42]

There is surprisingly little evidence in the rodent literature to support the seeming relationship between perinatal organochlorine pesticides and offspring obesity. *In utero* exposure to HCB did not consistently affect the body weights of rats across their 100 days of life.[64] Similarly, adult female rats exposed to HCB did not experience a change in body mass after 1 month.[65,66] Mice prenatally exposed to 100 mg DDT/kg maternal body weight/day had higher body weights in the week after birth when the study ended.[67] Male rats exposed to DDT during puberty had no change in body weights from puberty to 12 weeks of age when the study ended.[68] Likewise, female rat pups exposed to DDT throughout their gestation and nursing had no change in body weights through 6 weeks old.[69] None of these studies examined fat mass. They also did not observe animals through middle age, when obesity is more likely to be evidenced.

*There is surprisingly little evidence in the rodent literature to support the seeming relationship between perinatal organochlorine pesticides and offspring obesity. However, none of the relevant studies observed animals through middle age, when obesity is more likely to be evidenced.*

Despite largely null findings of developmental DDT effects on postnatal growth experimentally, one perinatal DDT study stands out in light of

DOI:10.1002/MSJ

recent obesity research. Rats prenatally exposed to 50 mg DDT/kg body weight/day for 3 days had transient fetal growth restriction, yet birth weights were similar to control rats.[70] When this same exposure paradigm was used across various postnatal windows, lactational transfer of DDTs also caused no change in offspring body mass.[70] Although no changes in offspring liver weights were observed, late gestational or lactational exposure to DDT resulted in excessive and disorganized endoplasmic reticulum, as well as excess lipid droplets and a higher RNA/DNA ratio in hepatocytes as early as the day of birth.[70] What is striking about this study is that nearly 30 years later, it was discovered that endoplasmic reticulum stress, which can result from excess protein translation, is tightly coupled to obesity.[71,72]

Adult primate research suggests that the association between prenatal DDE and offspring obesity in humans may be due to effects of DDE on lipid metabolism. Rhesus monkeys exposed to DDT had decreased cholesterol and phospholipids in the brain, increased hepatic lipogenesis, increased hepatic triglycerides, as well as increased cholesterol and triglycerides in both serum and adipose.[73,74]

## Polyfluoroalkyls

Perfluoroalkyls (PFOA) are surfactants that act through PPAR$\alpha$ and PPAR$\gamma$, and perhaps other nuclear receptors.[75,76] The PPARs are critical in the regulation of fat metabolism and storage, adipocyte differentiation, and insulin sensitivity.[77] As has been observed in other cross-sectional studies of POPs reviewed here, perfluoroalkyls in adolescents are associated with lower waist circumference or have no association with either waist circumference or BMI, whereas perfluoroalkyls in adults are associated with increased BMI and waist circumference (Table 2).[78–80] Although the direction of causality cannot be inferred from cross-sectional studies, 2 adult studies using retrospective BMI data with PFOA and PFOS in serum suggest that positive associations between adiposity and PFOAs may reflect unique exposure of obese people to PFOAs and/or unique PBPK of PFOAs in obese people.[81,82]

Despite the lack of prospective studies in humans of developmental exposure to PFOAs and offspring body mass and fat, mice exposed to PFOAs echo the theme seen with POPs reviewed above, where low developmental doses cause obesity and high doses do not. Mice exposed to low levels of PFOAs *in utero* had significantly increased body mass by 10 weeks old, which persisted through midlife.[24]

*Mice exposed to low levels of perfluoroalkyls in utero had significantly increased body mass by 10 weeks old, which persisted through midlife.*

When these mice were 18 months old, there was an inverse and direct dose-response relationship between *in utero* PFOA doses and abdominal white and brown adipose tissue masses, respectively.[24] However, mice exposed to high doses of PFOAs during gestation had decreased body mass.[24,83,84] As to be expected from observations of adult human exposure to PFOAs, mice exposed to PFOAs as adults experienced no change in body mass or fat mass across PFOA doses and ages.[24]

## Polybrominated Diphenyl Ethers

Many kinds of brominated flame retardants have been used in consumer products for the past 30+ years to provide fire safety. One of the major classes, the polybrominated diphenyl ethers (PBDEs), were used in many products in the US and either have been or are being voluntarily phased out, and they are banned in the European Union. Levels of PBDEs in children are 2–6× higher than those found in adults across the world.[85–90] There are no known studies of developmental exposures to PBDEs and obesity in humans. As in other cross-sectional observations of POPs, women with high BMI have higher levels of PBDEs.[91,92]

Experimental studies have linked developmental exposure to the commercial penta-PBDE mixture, or to congeners mainly present in that mixture, to changes in body weight, yet the direction of change is inconsistent and observation periods of most of the studies are quite short.[47,56,93–95] In the longest study of developmental PBDE exposure to look at body weights, male mice exposed to BDE47 (2,2′,4,4′-tetraBDE) 10 days after birth had increased body weights from PND 47 until the end of the study, at 4 months of age.[93] The effects of BDE47 were not as clean-cut in another study.[95] When rats were exposed to 200 μg BDE47/kg body weight every 5 days from GD 15 to PND 20, their offspring weighed more from birth to the end of the study at PND 47 (when $P = 0.06$).[95] Because these BDE47-exposed offspring were also consistently longer, their BMI was lower than controls on PND 15. In contrast, if the same protocol was used for 2 μg BDE47/kg body weight doses, offspring body weights and lengths did not differ from controls, but their BMIs

DOI:10.1002/MSJ

**Table 2.** *Child and Adolescent Obesity and Exposures to Chemical Classes Containing PPAR Agonists Organized by Chemical Class with Ascending Ages per Chemical.*

| Chemical | Age at Exposure (n) | Design | Duration of Follow-Up (Sex) | Exposure | Outcome |
|---|---|---|---|---|---|
| Perfluoroalkyls | | | | | |
| PFOA[78] | 12–19 years (585) | Cross-sectional | 0 (M/F) | 0.1–37.3 μg/L serum* | NS BMI, NS WC |
| PFOA[79] | 12–19 years (474) | Cross-sectional | 0 (M/F) | 1.5 ± 0.1 log ng/mL serum | Decreased WC (OR = 0.6 per log ng/mL) |
| PFOS[78] | 12–19 years (322) | Cross-sectional | 0 (M) | 1.4–392.0 μg/L serum* | Decreased BMI ($\beta^{\dagger} = -2.8$ kg/m$^2$ between Q4 and Q1), decreased WC ($\beta^{\dagger} = -9.0$ cm between Q4 and Q1) |
| PFOS[78] | 12–19 years (263) | Cross-sectional | 0 (F) | 1.4–392.0 μg/L serum* | NS BMI, decreased WC ($\beta^{\dagger} = -4.8$ cm between Q4 and Q1) |
| PFOS[79] | 12–19 years (474) | Cross-sectional | 0 (M/F) | 3.11 ± 0.05 log ng/mL serum | Decreased WC (OR = 0.4 per log ng/mL) |
| PFNA[78] | 12–19 years (585) | Cross-sectional | 0 (M/F) | 0.1–10.3 μg/L serum* | NS BMI, NS WC |
| PFNA[79] | 12–19 years (474) | Cross-sectional | 0 (M/F) | −0.3 ± 0.1 log ng/mL serum | NS WC |
| PFHxS[78] | 12–19 years (585) | Cross-sectional | 0 (M/F) | 0.2–27.1 μg/L serum* | NS BMI, NS WC |
| PFHxS[79] | 12–19 years (474) | Cross-sectional | 0 (M/F) | 0.9 ± 0.1 log ng/ml | Decreased WC (OR = 0.6 per log ng/mL) |
| Short-lived, but ubiquitous, pollutants | | | | | |
| MEP[99] | 6–9 years (90) | Cross-sectional | 0 (F) | 5.3–2580.0 μg/L urine | NS BMI |
| MEP[98] | 6–11 years (656) | Cross-sectional | 0 (M/F) | 0.6–9043.6 μg/L urine | NS BMI and WC |
| MEP[98] | 12–19 years (662) | Cross-sectional | 0 (M) | 0.6–12,359.0 μg/L urine | NS BMI, NS WC |
| MEP[98] | 12–19 years (682) | Cross-sectional | 0 (F) | 5.9–39,631.7 μg/L urine | Increased BMI ($\beta^{\dagger} = 1.7$ kg/m$^2$ between Q4 and Q1), increased WC ($\beta^{\dagger} = 4.1$ cm between Q4 and Q1) |
| MECPP[99] | 6–9 years (90) | Cross-sectional | 0 (F) | 5.9–2260.0 μg/L urine | NS BMI |
| MEHHP[99] | 6–9 years (90) | Cross-sectional | 0 (F) | 1.4–1699.0 μg/L urine | NS BMI |
| MEHHP[98] | 6–19 years (1030) | Cross-sectional | 0 (M/F) | 0.7–2118.3 μg/L urine | NS BMI, NS WC |
| MEHP[99] | 6–9 years (90) | Cross-sectional | 0 (F) | 0.6–110.0 μg/L urine | NS BMI |
| MEHP[98] | 6–11 years (656) | Cross-sectional | 0 (M/F) | 0.6–9043.6 μg/L urine | NS BMI, NS WC |
| MEHP[98] | 12–19 years (662) | Cross-sectional | 0 (M) | 0.7–273.4 μg/L urine | NS BMI, NS WC |
| MEHP[98] | 12–19 years (682) | Cross-sectional | 0 (F) | 0.7–549.2 μg/L urine | Decreased BMI ($\beta^{\dagger} = -1.5$ kg/m$^2$ between Q4 and Q1), NS WC |
| MBzP[99] | 6–9 years (90) | Cross-sectional | 0 (F) | 0.1–191.0 μg/L urine | NS BMI |
| MBzP[98] | 6–19 years (2000) | Cross-sectional | 0 (F) | 0.2–1685.0 μg/L urine | NS BMI, NS WC |
| MiBP[99] | 6–9 years (90) | Cross-sectional | 0 (F) | 0.2–144.0 μg/L urine | NS BMI |
| MCPP[99] | 6–9 years (90) | Cross-sectional | 0 (F) | 0.4–76.9 μg/L urine | NS BMI |
| MBP[99] | 6–9 years (90) | Cross-sectional | 0 (F) | 0.3–363.0 μg/L urine | NS BMI |

(*continued overleaf*)

DOI:10.1002/MSJ

DOI:10.1002/MSJ

**Table 2.** *(Continued).*

| Chemical | Age at Exposure (n) | Design | Duration of Follow-Up (Sex) | Exposure | Outcome |
|---|---|---|---|---|---|
| MBP[98] | 6–19 years (2000) | Cross-sectional | 0 (M/F) | 0.6–2595.3 μg/L urine | NS BMI, NS WC |
| MEOHP[99] | 6–9 years (90) | Cross-sectional | 0 (F) | 1.3–1070.0 μg/L urine | NS BMI |
| MEOHP[98] | 6–19 years (2000) | Cross-sectional | 0 (M/F) | 0.8–1380.1 μg/L urine | NS BMI, NS WC |
| BPA[99] | 6–9 years (90) | Cross-sectional | 0 (F) | <0.2–26,700.0 μg/L urine | Decreased BMI (≥85th % tile group mean = 41.8 μg/L, <85th % tile group mean = 26.9 μg/L) |
| Thiazolidinediones | | | | | |
| Pioglitazone[163] | 14 ± 1.9 (35) | Randomized controlled trial | 6 months | 15 mg orally daily for 3 weeks, 30 mg daily thereafter if tolerated | Increased change in BMI $z$ score‡ (pioglitazone group mean = 0.3 kg/m$^2$ $z$ score,‡ placebo group mean = 0.0 kg/m$^2$ $z$ score‡) |
| Rosiglitazone[164] | 13.6 ± 1.6 SD (36) | Randomized controlled crossover trial | 24 weeks each, with 4-week washout | 4 mg orally twice daily | NS BMI-SDS, NS WC, NS skinfolds |

NOTE: Evidence is presented by chemical class with ascending ages per chemical.

**Abbreviations:** BMI, body mass index; BPA, bisphenol A; MBP, mono-n-butyl phthalate; MBzP, mono-benzyl phthalate; MCPP, mono(2-ethylhexyl)phthalate; MEHP, mono-2-ethylhexyl phthalate; MEHHP, mono-2-ethyl-5-hydroxyhexyl phthalate; MEOHP, mono-2-ethyl-5-oxohexyl phthalate; MEP, monoethyl phthalate; MiBP, mono-isolbutyl phthalate; MMP, monomethyl phthalate; NS, not significant; OR, odds ratio; PFHxS, perfluorohexane sulfonic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfate; PFNA, perfluorononanoic acid; PPAR, peroxisome proliferator activated receptor; SD, standard deviation; SDS, standard deviation score; WC, waist circumference.

*Range includes adults.

†Change in the outcome (eg, BMI, BW) per 1-unit change in the exposure.

‡Descriptive statistic used to describe variability.[38]

were higher than those of controls at PND 5 and lower than those of controls at PND 15 and 25.[95] Kestrels, a bird of prey, exposed to a mixture of penta-PBDEs *in ovo* and during development weighed more, gained weight more quickly, and ate more as nestlings.[94] However, during the first 3–4 weeks of life, body weights of mouse offspring were unaffected by maternal exposure to PBDE99 (2,2′,4,4′,5-pentaBDE) (0.6, 6, or 30 mg/kg body weight/day GD 6–PND 21; or 1 or 10 mg/kg body weight/day GD 10–18).[47,56] These PBDE-induced growth changes might be linked to changes in lipid metabolism. For instance, developmental exposure to BDE47 increased cholesterol levels in shrimp, and exposure to a commercial penta-PBDE mixture in rats increased lipolysis in their isolated adipocytes.[96,97]

## Short-Lived, but Ubiquitous, Pollutants

### Phthalates

Phthalates are used in plastics and fragrances and are known agonists of PPAR$\alpha$, PPAR$\beta$, and PPAR$\gamma$.[77] In adolescent girls of the 1999–2002 NHANES, BMI and waist circumference increases were associated with increasing urinary monoethyl phthalate (MEP) levels but BMI decreased in association with monoethyl-hexyl phthalate (MEHP; Table 2).[98] Other urinary phthalates detected in the 1999–2002 NHANES were not associated with these measures of adiposity in children or adolescents (Table 2).[98] In a smaller cross-sectional study of adolescent girls, urinary phthalates were not associated with BMI above the national 85th percentile (Table 2).[99] However, in contrast to the trend seen with cross-sectional studies of POPs, cross-sectional studies of phthalate metabolites in the urine of adults show that the metabolites are associated with increased waist circumference and BMI.[98,100]

Cell-culture experiments support a potential role of developmental phthalate exposures in obesity. For instance, MEHP and dicyclohexyl phthalate induced adipogenesis in the adipocyte differentiation 3T3L1 cell-culture model.[101–103] Unfortunately, there are no known *in vivo* studies of developmental phthalate exposure and body mass outcomes in animals, although adult rodents shed some light on the potential role of diethylhexyl phthalate (DEHP) in human obesity. In several studies, adult rodents exposed to DEHP did not increase in body and/or fat mass.[77,104,105] Yet when mouse PPAR$\alpha$ was replaced by humanized PPAR$\alpha$, DEHP increased fat mass in adult mice, suggesting that DEHP could increase fat mass in humans.[77]

### Bisphenol A

Bisphenol A (BPA) is used in a variety of hard plastics, can linings, and thermal papers, and is a estrogen receptor agonist.[106] BPA activates PPAR and its derivative, BPA diglycidyl ether, is the only known PPAR$\gamma$ antagonist and also acts as a PPAR$\gamma$ agonist.[107] The only epidemiology study that examined the association of BPA and obesity in children used cross-sectional data on adolescent girls; being above the national 85th percentile of BMI for age and sex was associated with less BPA in urine (Table 2).[99] A similar finding was reported in adults of the 2003–2004 NHANES.[108]

Numerous rodent studies have reported on the effects of developmental exposures to BPA and body mass (Table 3). Readers are referred to recent reviews for discussion of the obesogenic properties of BPA in experimental models published prior to 2010; however, it should be noted here that differences between similar studies have been attributed to estrogenic contamination of feed, cages, and water bottles.[8,109] Rodent BPA studies published in 2010, as well as *in vitro* studies, are described below.

Mice exposed to low BPA levels from mid- to late- gestation had significantly increased body mass at birth and weaning, whereas mice exposed to relatively high (100 μg/kg body weight) BPA from mid to late gestation had significantly decreased body mass from birth through weaning.[110] Thereafter, the body weights of male offspring exposed to BPA *in utero* did not differ from control mice until 6 months of age, when they were no longer followed. However, female mice exposed to either BPA dose weighed significantly less than control mice at 3 months of age.[110]

In another study, pups from dams that ate food containing ecologically relevant levels of BPA weighed more at weaning. Male and female offspring had similar body weights as did controls from weaning to 9 weeks old when the study ended; however, females had lower fat mass compared with controls at 9 weeks.[111] Rats exposed to BPA *in utero* experienced little effect of BPA on body weights through PND 72, although there were some transient decreases in body weights of males and females in the highest BPA dose groups.[112] Adolescent male rats that were exposed to high doses of BPA had decreased body weights at the end of the BPA treatment period, when they were 10 weeks old.[113]

*In vitro* studies support the influence of early life BPA exposure on obesity. For instance, when 2-cell mouse embryos were exposed to 1 nM or 3 nM BPA, the rate of development into blastocysts was accelerated, yet this rate was decreased when 2-cell mouse embryos were exposed to 100 μM BPA.[114]

DOI:10.1002/MSJ

DOI:10.1002/MSJ

**Table 3.** *Immature Rodent Exposures to Chemical Classes Containing PPAR Agonists and Obesity with Ascending Ages per Chemical.*

| Chemical | Exposure Window | Species and Sex | Duration of Follow-Up | Dose | Outcome |
|---|---|---|---|---|---|
| Perfluoroalkyls | | | | | |
| PFOA[24] | GD 1–17 | *Mus* F | 18 months old | 0.01, 0.1, or 0.3 mg/kg BW daily* | Increased BW 20–37 weeks old,† increased WAT 18 months old, decreased BAT 18 months old |
| PFOA[24] | GD 1–17 | *Mus* F | 18 months old | 1, 3, or 5 mg/kg BW daily* | Decreased BW various ages, decreased WAT 18 months old, increased BAT 18 months old |
| PFOA[84] | GD 7–17, GD 10–17, GD 13–17, or GD 15–17 | *Mus* M | 35 weeks old | 3, 5, 10, or 20 mg/kg BW daily* | Decreased BW through PND 71 |
| PFOA[84] | GD 7–17, GD 10–17, GD 13–17, or GD 15–17 | *Mus* F | 35 weeks old | 3, 5, 10, or 20 mg/kg BW daily* | Decreased BW until weaning, increased BW 23 weeks and older if exposed GD 13–17 |
| PFOA[83] | 3–7 weeks | *Mus* F | 7 weeks old | 10 mg/kg BW daily, 5 days/week* | Decreased BW 7 weeks |
| PFOA[83] | 3–7 weeks | *Mus* F | 7 weeks old | 1 or 5 mg/kg BW daily, 5 days/week* | NS BW |
| PFOA[24] | 8–10.5 weeks | *Mus* F | 18 months old | 0.01, 0.1, 0.3, 1, 3, or 5 mg/kg BW daily* | NS BW, NS WAT, NS BAT |
| Short-lived, but ubiquitous, pollutants | | | | | |
| BPA[109] | 1 week pre-conception–weaning | *Mus* M | PND 28 | 5 or 10 μg/ml‡ ≅ 1.2 mg total | NS BW |
| BPA[115] | Preimplanted embryos | *Mus* M/F | PND 21§ | 1 nM or 100 μM | Increased BW PND 21 |
| BPA[111] | GD 0–PND 21§ | *Mus* M/F | 14 weeks old | 1 μg/kg¶# ≅ 0.25 μg/kg BW | Increased BW 3 weeks; NS BW 4–14 weeks; decreased fat if fed HFD 14 weeks |
| BPA[112] | GD 0–PND 21§ | *Rattus* M | PND 21 | 0.15 ppm¶ | Increased BW PND 21 |
| BPA[112] | GD 0–PND 21§ | *Rattus* M | PND 72 | 1.5 ppm¶ | NS BW |
| BPA[112] | GD 0–PND 21§ | *Rattus* F | PND 72 | 0.15, 1.5, or 75 ppm¶ | NS BW |
| BPA[112] | GD 0–PND 21§ | *Rattus* M | PND 72 | 75, 750, or 2250 ppm¶ | Decreased BW various days PND 4–21 |
| BPA[112] | GD 0–PND 21§ | *Rattus* F | PND 72 | 750 or 2250 ppm¶ | Decreased BW various days PND 4–21 |
| BPA[110] | GD 3–PND 21§ | *Mus* M/F | PND 21 | 2 or 200 μg/kg BW/day¶ | NS BW |

(*continued overleaf*)

**Table 3.** *(Continued).*

| Chemical | Exposure Window | Species and Sex | Duration of Follow-Up | Dose | Outcome |
|---|---|---|---|---|---|
| BPA[110] | GD 9–16 | *Mus* M | 6 months old | 10 μg/kg BW** | Increased BW birth, increased BW weaning |
| BPA[110] | GD 9–16 | *Mus* M | 6 months old | 100 μg/kg BW** | Decreased BW birth–weaning |
| BPA[110] | GD 9–16 | *Mus* F | 6 months old | 10 or 100 μg/kg BW** | Decreased BW 3–6 months old |
| BPA[185] | GD 9–20 (partuition) | *Mus* F | 12 months old | 25 or 250 μg/kg BW†† | Increased BW 9 months old |
| BPA[150] | GD 10–PND 30 | *Mus* M | PND 31 | 1 μg/mL‡ ≍ 0.26 mg/kg BW | NS BW, NS WAT PND 31 |
| BPA[150] | GD 10–PND 30 | *Mus* M/F | PND 31 | 10 μg/mL‡ ≍ 2.72 mg/kg BW | Increased BW, increased WAT PND 31 |
| BPA[150] | GD 10–PND 30 | *Mus* F | PND 31 | 1 μg/mL‡ ≍ 0.26 mg/kg BW | Increased BW, increased WAT PND 31 |
| BPA[150] | GD 10–PND 30 | *Mus* F | PND 31 | 10 μg/mL‡ ≍ 2.72 mg/kg BW | Increased BW PND 31 |
| BPA[146] | GD 11–17 | *Mus* M | PND 60 | 2 μg/kg BW** | NS BW |
| BPA[186] | GD 11–17 | *Mus* M/F | PND 22§ | 2.4 μg/kg BW* | Increased BW PND 22 |
| BPA[146] | GD 11–17 | *Mus* F | PND 60 | 2 or 20 μg/kg BW** | Decreased BW various days |
| BPA[147] | GD 11–17 | *Mus* F | PND 310 | 2 or 20 μg/kg BW* | NW BW |
| BPA[146] | GD 11–17 | *Mus* M | PND 60 | 20 μg/kg BW** | Decreased BW various days |
| BPA[187] | GD 12–PND 21§ | *Rattus* M | PND 90 | 2.4 μg/kg BW* | Increased BW PND 90 |
| BPA[149] | GD 15–19 | *Mus* | 16 weeks old | 0.5 or 10 mg/kg BW** | Increased BW |
| BPA[188] | GD 21–PND 21§ | *Rattus* F | 16 months old | 1 or 10 mg/L‡ ≍ 0.1 or 1.2 mg/kg BW | Increased BW various days |
| BPA[188] | GD 21–PND 21§ | *Rattus* M | 3 months old | 1 or 10 mg/L‡ ≍ 0.1 or 1.2 mg/kg BW | Increased BW various days |
| BPA[189] | PND 5 | *Rattus* M | 8 weeks old | 0.02, 0.2, 2, or 20 μg total‡‡ | NS BW |
| BPA[186] | PND 21–90 | *Rattus* M | PND 90 | 2.4 μg/kg BW* | NS BW |
| BPA[113] | 4–10 weeks | *Rattus* M | 10 weeks old | 20 mg/kg BW** | NS BW |
| BPA[113] | 4–10 weeks | *Rattus* M | 10 weeks old | 100 or 200 mg/kg BW** | Decreased BW 10 weeks |
| Metals | | | | | |
| TBT[123] | "Pregnancy"–PND 21§ | *Mus* M | PND 21 | 15 or 50 ppm‡ | Decreased BW PND 7 |
| TBT[122] | GD 0–PND 21§ | *Rattus* F | 15 weeks old | 125 ppm¶§§ | Decreased BW 9–15 weeks |
| TBT[69] | GD 0–PND 21§ | *Rattus* F | 6 weeks old | 25 μg TBT/g¶ | Decreased BW PND 28 and 6 weeks |
| TBT[120] | GD 4–PND 21§ | *Rattus* M/F | PND 23 | 6 mg/kg BW* | Decreased BW PND 1–2 |
| TBT[120] | GD 4–PND 21§ | *Rattus* M/F | PND 23 | 2 mg/kg BW* | NS BW |
| TBT[121] | GD 6–17 | *Mus* M/F | PND 55 | 7.5 mg/kg BW* | NS BW |
| TBT[121] | GD 6–17 | *Mus* M/F | PND 55 | 15 mg/kg BW* | Decreased BW PND 1 |
| TBT[119] | GD 12–18 | *Mus* M/F | 10 weeks old | 0.05 or 0.5 mg/kg BW | NS BW, increased WAT 10 weeks |
| TBT[125] | PND 24–45 | *Mus* M | PND 84 | 0.05 mg/kg BW every 3 days* | Increased BW PND 56–84 |
| TBT[125] | PND 24–45 | *Mus* M | PND 84 | 0.5 mg/kg BW every 3 days* | NS BW |

(*continued overleaf*)

DOI:10.1002/MSJ

DOI:10.1002/MSJ

**Table 3.** *(Continued).*

| Chemical | Exposure Window | Species and Sex | Duration of Follow-Up | Dose | Outcome |
|---|---|---|---|---|---|
| TBT[126] | "After quarantine" (began PND 21)–45 days later | *Mus* M | 45 days after treatment | 0.5 or 50 μg/kg BW every 3 days* | NS BW, NS fat mass |
| TBT[126] | "After quarantine" (began PND 21)–45 days later | *Mus* M | 45 days after treatment | 5 μg/kg BW every 3 days* | Increased BW gain, increased fat mass |
| TBT[68] | 6–12 weeks | *Rattus* M | 12 weeks old | 0.04 ng/g¶ | Increased BW 8–12 weeks |
| TBT[122] | 9–15 weeks | *Rattus* F | 15 weeks old | 125 ppm diet¶¶ | Decreased BW 9–15 weeks |
| Thiazolidinediones | | | | | |
| Pioglitazone[165] | 7–12.5 weeks | *Rattus* M | 12.5 weeks old | 12 mg/kg BW* | Increased BW 7.5–12.5 weeks |
| Pioglitazone[165] | 10.5–15 weeks | *Rattus* M | 15 weeks old | 12 mg/kg BW* | Increased BW 12–15 weeks |
| Rosiglitazone[166] | PND 21–60 | *Rattus* F | PND 60 | 11 μmol¶ | Increased WAT PND 60, increased BAT PND 60 |
| Englitazone[168] | GD 16–21 | *Rattus* M/F | PND 0 | 50 mg/kg BW* | Decreased BW PND 0 |

NOTE: Evidence is presented by chemical class with ascending ages and doses per chemical.
**Abbreviations:** BAT, brown adipose tissue; BMI, body mass index; BPA, bisphenol A; BW, body weight; GD, gestation day; HFD, high fat diet; NS, not significant; OR, odds ratio; PFOA, perfluorooctanoic acid; PND, postnatal day; PPAR, peroxisome proliferator activated receptor; ppm, parts per million; TBT, tributyltin; WAT, white adipose tissue; WC, waist circumference.
*Oral gavage.
†Last measurement of study.
‡Water.
§Weaning.
In vitro.
¶Diet.
#Dams ate more diet when it contained BPA PND 14–21.
**Subcutaneous.
††Osmotic pump.
‡‡Intracisternal.
§§Dams ate less diet when it contained TBT.
Intraperitoneal.

Further, when 2-cell mouse embryos were exposed to either 1 nM or 100 μM BPA, they were heavier than controls at weaning (end of study).[115] In another series of experiments, BPA induced the differentiation of 3T3-L1 fibroblasts into adipocytes.[103,116,117]

## Metals

### Organotins

Organotins are used in plasticizers, slimicides, fungicides, antifoulants, catalysts, and stabilizers.[9] Though organotins are found in humans, there are no known studies of their relationship with body mass or adiposity in humans to date.[9] The experimental evidence for tributyltin (TBT) and triphenyltin (TPT) as potential obesogens has been reviewed recently, and readers are referred to that review for additional discussion of organotins research.[9]

TBT and TPT are retinoid X receptor and PPARγ agonists.[118,119] Acute prenatal and postnatal exposure to TBT (sufficient to increase mortality) decreases postpubertal growth in mice (Table 3).[120–122] At lower doses, prenatal TBT exposure appears to have little to no impact on body mass while increasing adipose mass. Peripubertal exposure to TBT seems to increase the likelihood of increases in both body and fat mass.

Neonatal mice exposed to TBT *in utero* had greater Oil Red O staining (indicative of lipid droplets) in their livers, testis, and adipose tissues.[119] After cross-fostering with untreated lactating mice, these mice had similar body masses, but males exposed to TBT *in utero* had 20% increased adipose mass over controls in adulthood (Table 3).[119] Similar TBT exposure levels *in utero* decreased body weights of male mouse pups in the first week after birth, but not in the second or third weeks after birth (Table 3).[123] Likewise, female rat pups exposed to TBT throughout their gestation and nursing had significantly reduced body weights at 4 and 6 weeks old (Table 3).[69] Unfortunately, these later 2 studies did not evaluate fat mass or monitor the rodents into adulthood.[69,123]

In another set of experiments where mice were exposed to TBT *in utero*, more of their multipotent stem cells differentiated into adipocytes when collected from adult mice compared with similarly collected *ex vivo* cells from vehicle-treated mice.[124] This resulted in a greater lipid accumulation within stem cells-turned-adipocytes that were from mice prenatally exposed to TBT compared with vehicle-treated mice.[124] Further, the stem cells from mice exposed to TBT *in utero* had a greater propensity to become lipid-filled adipocytes when exposed to more TBT or the diabetes drug rosiglitizone, another PPARγ agonist. This increased adipogenic capacity may have resulted in a TBT-induced shift in cell population; prior to experimentally induced differentiation of adipocytes, there were 6% more preadipocytes detected among *ex vivo* cells from mice prenatally exposed to TBT compared with mice exposed to vehicle.[124] Tributyltin also appears to act as a developmental obesogen at lower doses in nonmammal animal models; it caused a dose-dependent increase in ectopic adipocyte formation around the gonads of male and female *Xenopus* that were exposed as tadpoles.[119]

Male mice exposed to TBT during puberty had increased body mass, associated with increased relative fat mass (Table 3).[125,126] Similar observations were also seen in male rats (Table 3).[68] In rats exposed to TBT *in utero* through adulthood, the trend of body mass and fat is less consistent than seen in other TBT developmental exposure studies; male rats had a small decrease in body mass, whereas 2 other studies found opposite effects of TBT exposure on the body weights of female rats.[127]

Cell-culture models support a role of developmental exposure to organotins in obesity. TBT also induces adipogenesis through PPARγ in multipotent stem cells of mice and humans.[124] Both TBT and TPT induce differentiation of 3T3-L1 adipocytes.[103,118,119,128]

### Lead

Lead poisoning is associated with developmental neurotoxicity. There is some evidence that lead exposure may also influence the risk of obesity, but most human studies do not support a positive association between developmental lead exposure and obesity. Lead levels in the teeth of male and female children (mean age 7.4 years) in the US were positively associated with their BMI measured at the same time.[129] These childhood dentin lead levels increased as BMI increased from the beginning of the study period to BMI in young adulthood (mean age 20.5 years).[129] However, the lead levels in patella and in tibia, which reflect recent lead exposure and long-term cumulative lead exposure, respectively, of these first-grade and second-grade children (mean age 7.4 years) were not associated with change in BMI measured in young adults.[129,130] A cross-sectional study found no association between blood lead levels and obesity in 11-year-olds,[131] which are not associated in adult women either.[132] Another study of adults showed a marginally significant inverse dose-response relationship between age-adjusted patella lead levels, which reflect recent exposures, during adulthood and abdominal obesity

DOI:10.1002/MSJ

($P = 0.07$).[130,133] Animal research is consistent with an early-life susceptibility to lead-associated adiposity and suggests there is an effect of gender: gestational exposure to lead increased the body mass of male but not female middle-aged mice.[134]

## Air Pollution: Cigarette Smoke and Diesel Exhaust

Prenatal maternal smoking is associated with increased occurrence of overweight among children and early adolescents.[21,135] There is also evidence that prenatal maternal smoking increases the odds of obesity in children.[136] The BMI SDS of toddlers was also associated with ever smoking among their mothers.[41] In another study, prenatal maternal smoking was not associated with adiposity measured by magnetic resonance imaging during early adolescence in males and females.[137] However, during late puberty, adolescents exposed to maternal prenatal smoking had 26% and 33% higher subcutaneous and intra-abdominal fat, respectively, than did their unexposed peers.[137] These results were independent of sex, age, and height.[137] Parental smoking was also associated with increased overweight and obesity among their children in a cross-sectional study.[135]

*During late puberty, adolescents exposed to maternal prenatal smoking had 26% and 33% higher subcutaneous and intra-abdominal fat, respectively, than did their unexposed peers.*

When mice were exposed to cigarette smoke while pregnant, the influence of the cigarette smoke on the body weights of their offspring was gender-dependent and diet-dependent.[138,139] Adult female offspring fed a normal diet had significantly increased body weights if exposed to cigarette smoke *in utero* compared with unexposed females, but cigarette smoke did not impact body weights of females fed a high fat diet for 2 weeks.[138] Adult male offspring exposed to cigarette smoke *in utero* had a higher body weight than control-treated males if fed a high fat diet, but there was no cigarette-smoking effect on male body weight if males ate a normal diet.[138] Male rats exposed to nicotine *in utero* had significantly increased body mass and white adipose tissue mass at weaning and through adulthood.[139] There was also evidence of adipocyte hypertrophy in the white adipose tissue mass at weaning. *In utero* nicotine exposure did not change food intake or energy expenditure. However, nicotine exposure was associated with higher food efficiency (food intake relative to body weight increase), decreased physical activity, decreased brown adipose tissue mass, and decreased thermogenesis.[139] None of these *in utero* nicotine effects were evident in female offspring.[139] Adult male (females not tested) mice exposed to the cigarette smoke and diesel exhaust constituent benzo[*a*]pyrene had increased body weights and weight gain compared with unexposed mice.[140] In another study, the longer that adult male rats were exposed to diesel exhaust, the greater the increase in their body weights.[141] These effects have not been reproduced in cell culture, where differentiation of 3T3-L1 preadipocytes, as well as their lipid accumulation, was decreased dose-dependently up to the equivalent exposure to 1 pack of cigarettes.[142]

## Pharmaceuticals

### Diethylstilbestrol

Diethylstilbestrol (DES) is a synthetic estrogen. Much of the evidence for DES as an obesogen has been produced in 1 laboratory.[143] Female mice exposed to 1 μg DES/kg body weight/day during PND 1–5 had increased body weight and fat mass as adults.[144] This was not seen in males under the same conditions. Mice exposed to 1 mg DES/kg body weight/day during PND 1–5 lost weight during treatment, but as a result of rapid compensatory growth during peripuberty, also had increased body weight and fat mass as adults. The increased body mass due to neonatal DES exposure persisted throughout adulthood but was no longer statistically significant when mice were 18 months old.[143]

Shorter studies of perinatal DES exposure have found increased, decreased, or no change in body masses of rodents in doses ranging from 0.02 to 10 μg DES/kg body weight/day and found consistently decreased body mass at 200 μg DES/kg body weight/day. Offspring exposed to 0.2 μg DES/kg maternal body weight/day GD 11–17 had increased body mass during the first week of life in one study but not another.[67,145] However, in other studies, maternal exposure to 0.02 or 0.2 μg DES/kg body weight during the same prenatal window decreased body weights of male and female offspring at various ages until PND 60 (measurements stopped).[146,147] Later prenatal (GD 16–18) exposure to 0.1 μg DES/kg body weight had no impact on offspring at day 21 or 60.[148] Male mice exposed to about 1 μg DES/kg body weight daily from conception to weaning had lower body and fat mass than did controls, whereas their female littermates had lower

DOI:10.1002/MSJ

fat mass compared with controls (monitored until 14 weeks old).[111] Maternal exposure to 2 μg DES/kg body weight prenatally increased birth weights of female neonates and had no impact on the body mass of female or male offspring thereafter (monitored until 60 days old).[146] Yet female mice whose mothers were exposed to 10 μg DES/kg weight daily during late gestation had increased body weights through 16 weeks of age when the study ended.[149] Offspring exposed to 200 μg DES/kg maternal body weight/day during either GD 11–17 or GD 16–18 had decreased body mass as neonates and at PND 60, respectively.[67,148] Some of the apparent inconsistencies in DES effects have been previously attributed to feeding a diet with estrogenic properties to both controls and DES-treated animals.[109,150]

## Antipsychotics

The number of office visits made by children and adolescents that included antipsychotic drug treatment increased 6-fold from 1993 to 2002; >90% of these prescriptions are atypical antipsychotics (AAPs).[151] Atypical antipsychotics are associated with increased body weight and waist circumference, and children and adolescents have a higher risk than do adults in developing these adverse effects.[152–154] According to a Medicaid database review, children utilizing AAP therapy had more than double the odds of being diagnosed with obesity.[155] In a prospective study of children, all 4 AAP treatments examined were significantly associated with increased body weight, fat mass, BMI, and waist circumference.[156] For instance, in only 12 weeks, the mean increase in fat mass of children taking aripiprazole, olanzapine, quetiapine, and risperidone was highly significant, at 2.4, 4.1, 2.8, and 2.4 kg, respectively, whereas the change in fat mass of untreated children was a mere 0.4 kg.[156] Olanzapine was also associated with the greatest gain in body weight, BMI, and waist circumference.[156] Olanzapine and risperidone were associated with extreme weight gain in >90% and >40% of adolescents, respectively, in a small 12-week study.[154]

*In only 12 weeks, the mean increase in fat mass of children taking aripiprazole, olanzapine, quetiapine, and risperidone was highly significant, at 2.4, 4.1, 2.8, and 2.4 kg, respectively, whereas the change in fat mass of untreated children was a mere 0.4 kg.*

Surprisingly few studies of AAP effects on adiposity in immature rodents exist. Lactational exposure to olanzapine increased body mass and increased waist-to-hip ratios in male and female mouse offspring during the third and fourth weeks of life (end of study).[157] Similarly, both male and female mice exposed to risperidone via lactation had higher waist-to-hip ratios.[157] Yet only female mice exposed to risperidone had increased body mass during the fourth week of life.[157] Rats exposed to either olanzapine, risperidone, sulpiride, or haloperidol during puberty had significantly increased body weights and percent intra-abdominal fat.[158] However, pubertal exposure to ziprasidone did not cause these effects.[158] The adult rodent literature on the association between AAPs and weight gain has been recently reviewed.[159]

## Thiazolidinediones

Thiazolidinediones (TZDs), eg, rosiglitazone, troglitazone, and pioglitazone, are PPAR$\gamma$ agonists used to treat type 2 diabetes. They decrease insulin resistance, circulating triglycerides, and free fatty acids.[160] Paradoxically, the PPAR$\gamma$–agonist activity of TZD is also associated with increased body-weight gain in clinical trials of adults.[161,162] Few clinical trials of TZDs exist in children. In one clinical trial, pioglitazone increased BMI SDS in adolescents with type 1 diabetes (Table 1).[163] Another clinical trial reported that rosiglitazone treatment did not alter the BMI SDS, waist circumference, or skin folds of adolescents (Table 1).[164]

Animal studies favor a positive association between TZDs and obesity. Body-weight gain was substantially greater in rats that were exposed to pioglitazone in late puberty compared with unexposed rats.[165] Pioglitazone exposures beginning in late puberty nearly doubled fat-pad weight in these rats, while causing a more modest increase in fat-pad mass in older rats.[165] These effects on adiposity may have been mediated by increased food intake among rats exposed to pioglitazone.[165] Similarly, pubertal exposure to rosiglitazone increased brown and white adipose tissue mass of rats.[166] Adult chickens exposed to troglitazone also had increased fat mass; however, when the troglitazone exposure was confined to their first day of life, they had significantly less fat-pad mass and ate less at 1 and 2 months of age.[167] Consistent with this developmental finding, rats exposed to englitazone during late gestation gave birth to smaller pups.[168]

DOI:10.1002/MSJ

## DISCUSSION

Research on developmental obesogens is in its infancy, with the majority of developmental obesogen research reviewed here having been published within the last decade. There likely are other chemicals in the environment that increase risk of obesity and have yet to be recognized. These obesogens will be discovered among the tens of thousands of new synthetic chemicals invented and produced in the past half century. The majority of these materials have not been tested for toxicity despite public health interventions to reduce exposures to known toxic substances.

How else can developmental obesogens be identified, given the inherent budget and time limitations relative to the abundant numbers of chemicals in manufacturing, commerce, and waste streams? While the field of research on the chemical origins of childhood obesity is in its infancy, tools exist to strengthen its depth and breadth. Pre-existing literature and cell culture assays can serve as *in silico* and *in vitro* obesogen screens, respectively. Whole rodent studies can seek to validate screens with an emphasis on mechanism of action and phenotypic anchoring to human studies. Human studies are the best method to confirm the relevance of developmental obesogens to human populations. Specific research directions for each of these fields are enumerated below.

### Future Research Directions

#### Experimental Research

*In silico and in vitro screening.* 1) Existing pharmaceutical research may be an excellent *in silico* screen. Pharmaceuticals are frequently studied in randomized controlled trials, a "gold standard" epidemiology study design that is infrequently employed in studies of environmental chemicals due to ethical concerns. Obesogen researchers should be in the habit of reviewing published randomized controlled trials for evidence of obesity as a side effect. This review identifies a number of anti-psychotic and anti-diabetic drugs that are associated with increased obesity in children and adolescents, and in most cases the molecular mechanisms of these drugs are understood, even if the exact reason for the obesity side- effects are unknown.[152,169–171] Many chemicals are already known to influence people through the same pathways on which these drug classes act. These candidate obesogens should be prioritized for obesity research.

2) The use of adipocyte differentiation as a cell culture model to identify obesogens has important implications for *childhood* obesogen research in particular. The total number of adipocytes increases during development. However, the number of adipocytes in an adult are approximately constant whether they are lean or obese; significant weight gain or loss in adults is not accompanied by respective increases or decreases in adipocyte numbers, instead adipocyte size is correlated to adult adiposity (for further discussion see recent reviews[53,54]). These observations support the notion that the number of adipocytes a person will have is determined primarily during childhood. If the total body fat mass is a function of # adipocytes × adipocyte size, any chemical that increases adipocyte numbers in developing organisms has the potential to greatly increase the total body fat mass during maturity. Given the relevance of differentiation of adipocytes in childhood obesity, cellular screens of compounds that cause differentiation of multi-potent human stem cells or 3T3-L1 cells at environmentally relevant concentrations would be helpful to prioritize *in vivo* characterization of obesogens.

3) Cell based screens to identify new chemicals that act on candidate obesogenic receptors identified with *in silico* screens, such as the PPAR receptors, are also available to help identify candidate obesogens.[106] Because a substantial breadth of developmental obesogen evidence presented here relates to chemicals associated with PPAR binding and/or expression, *in vitro* screens that determine PPAR binding and expression by environmentally relevant levels of candidate obesogens would likely be useful to identify chemicals to be used for *in vivo* obesogen research. Such a screen could evaluate whether a cumulative addition model of additivity would be useful in testing mixtures of PPAR ligands in a modified version of the TEQ model of additivity, the PPAR equivalence (PPAREQ) model.

*In vivo validation.* Candidate obesogens that have been identified through *in silico* and/or *in vitro* research should be carefully selected for *in vivo* experimental research to 1) examine mechanisms of obesogens while 2) striving to employ experimental designs that will be relevant to human studies.

1) Obesogen experimentalists should use whole animals, or at least validate their cell culture models *in vivo*, for mechanistic research because metabolism is a multi-organ dynamic process. For instance, lipid homeostasis involves constant interaction between adipose tissue, liver, muscle, and the hypothalamus (Figure 1). All these tissues are potential targets of metabolic perturbation. Obesogens must be identified by examining energy balance because only a change in energy balance can change body mass. "Energy in" is burned, stored, or excreted and

DOI:10.1002/MSJ

mechanism of action studies should seek to evaluate these aspects of energy balance. Caloric intake should be quantified and controlled if divergent across treatment groups. If a change in body mass cannot be accounted for by a change in caloric intake, lipid and carbohydrate homeostasis should be dynamically tested and metabolic chamber experiments should identify activity, body temperature, and caloric content of feces. These tests would ideally occur before animals reach a state of obesity in order to identify initiating metabolic defects leading to obesity. Positive, as well as negative, controls should be included to be sure that the experiment has the power to detect a response.

2) Whole animal studies also need to be designed with human exposure studies in mind. Chemicals should be administered in environmentally relevant doses according to the route of human exposure, or as closely as possible. In deciding how to model exposure to ingested chemicals, the stress of oral gavage ought to be weighed against the potential drawbacks of mixing the exposure into food, such as potential confounding by changes in appetite. Finally, administered doses as well as internal measures of tissue dose, often whole blood- and serum- levels, must be reported to facilitate comparison with humans. For certain rapidly eliminated compounds, urinary concentrations may be appropriate to measure for animal/human comparisons. Phenotypically anchoring animal studies to human studies by measuring animal phenotypes that are relevant and measurable in humans will ultimately provide an opportunity to corroborate obesogen data across species. This does not mean it is sufficient to only measure body weight of animals, as some chemicals increase fat mass without changing body mass. Adipose tissue mass and distribution should be measured both *in vivo* using MRI and at study termination, which should extend past young adulthood.

## Human research

*Epidemiologic research* In order to strengthen the hypothesis that certain chemicals contribute to the risk of obesity, one would ideally want epidemiology studies that are designed with consideration of 1) PK and 2) non-linear dose-response.

1) If obesity modifies the PK of lipophilic chemicals, the direction of causal association between obesity and chemicals may be particularly unclear in cross-sectional studies. Ideal obesogen studies would be prospective longitudinal studies with clear separation between chemical exposure assessment and obese case ascertainment in order to delineate the causal direction of their association. Whenever possible, exposures should be measured *in utero* and in infancy, because this period of metabolic programming appears to be the most environmentally sensitive window for setting the lifetime metabolic trajectory. Although peripubertal exposure to either BPA or PFOA did not produce an obese phenotype in rodent studies reviewed here, it is noteworthy that half of the peripubertal TBT rodent studies and all of the peripubertal TZD rodent studies resulted in an obese phenotype (Table 3). Epidemiologists with peripubertal biological samples may wish to test the obesogen hypothesis also. Further, attempts should be made to quantify the odds or risk of an association between a chemical and obesity due only to the PK effects of obesity. This would allow epidemiologists to identify how strong an association between chemicals and obesity must be in order to be greater than the PK effect size. Such efforts will help dismiss the conclusion that the association between a chemical and obesity is merely an artifact of obesity's influence on the chemical's PK behavior.

2) Many of the research examples presented here demonstrate non-linear dose response between chemicals and body mass and/or adiposity. If chemicals are banned and/or human exposure levels are declining in some populations, it would be desirable to have exposures measured in samples collected prior to the time at which chemicals were banned and/or when human exposure levels peaked, in order to better understand the shape of the dose response curve. Such efforts will be critical in accurate assessment of risk across various populations with differing "background" levels of these chemicals. For instance, DDE and DDT levels are quite low in the general US population yet DDT and DDE levels are relatively high in populations where DDT is still used or was recently in use.[172] Similarly, PBDEs are in various stages of being phased out in the US and Europe but the highest exposure levels are seen in children living and working in electronic waste sites in other regions.[86,90]

*Clinical research* The most efficacious focus of clinical researchers interested in developmental obesogens is to 1) monitor obesity as a side- effect of prescribed medications, and 2) to make use of long-term relationships with pediatric patients.

1) Pediatricians have the opportunity to observe whether prescribed medications are associated with increased weight gain and excess change in growth trajectories. Converting the body weights of children into age- and sex- matched percentiles of standardized growth can greatly facilitate this endeavor. Careful observation of weight gain as a side- effect is particularly critical because there are conditions for

which few or no therapeutic clinical trials have been conducted in pediatric populations. Excess weight gain resulting from these off- label uses may be under-reported, thus pediatricians are encouraged to publish case- reports of such observations.

2) The possible effect of chemicals on the metabolic programming of obesity is great, yet there are very few studies of chemical exposures during prenatal and perinatal development which provide the information needed to assess later obesity due to the potentially long latency before obesity is evidenced. Given this, pediatricians are advised to obtain a brief history of occupational and environmental exposure from every patient and parent. If this initial screen raises suspicion of a child's exposure to a chemical that may be an obesogen or otherwise influence development, more detailed follow-up questions should be asked or consultation sought with a specialist in occupational and environmental medicine. Although many chemicals reviewed here are widely dispersed, the clinician is reminded when treating patients living or once living in malarial areas that the World Health Organization endorses indoor DDT spraying for malaria vector control.[172] While outside the scope of this review, the clinician is also alerted that the dysfunctional metabolic, immune, endocrine, and reproductive systems of obese children may also reduce their capacity to defend against toxic insults.[49,105,133,139,173–176] Thus the clinician must also seek to identify exposures that cause adverse effects in obese children that are not seen in lean children, in addition to seeking to identify obesogens.

## Closing remarks

Although the epidemiologic data on developmental obesogens are not yet clear, animal studies indicate that developmental obesogens do exist and numerous chemicals that are candidate obesogens are identified here. While no study could be expected to singly address all of our recommended research directions, prospective longitudinal cohorts are a powerful approach to obesogens research and would lead to translational studies that integrated some of our epidemiologic research suggestions with our experimental research suggestions.

An emerging unifying theme of obesogen effects reviewed here is the evidence of non-linear effects on body weight and adiposity. Specifically, many chemicals caused cachexia at high doses, but increased body mass and/or adipose mass at doses closer to the exposure range seen in humans. Historically, bench toxicology research has employed doses of substances log folds higher than observed human exposures in order to detect mortality and severe morbidities, e.g. cachexia, as endpoints using relatively few animals.[177] More obesogens will likely emerge as more "subtle" effects are detected at doses that more closely emulate human exposure levels.

Across different chemical classes reviewed here, numerous studies reported sex-specific effects. It is not clear whether these are true biological phenomena, spurious associations due to multiple testing, or artifacts of study design and publication bias (e.g. only examining/publishing data on one sex). Two primary facts support a biological underpinning to the gender specificity of obesogens. 1) Many candidate obesogens cause sex-specific toxic effects on sexual maturation, reproduction, and cancers. 2) There are well-known sex effects on fat regulation, including the regulation of adipose tissue distribution and leptin signaling by estrogen.[9,178]

Relative to body weight, children ingest more toxicants than do adults eating the same toxicant-contaminated diet.[179] Some obese children are likely at an even greater risk of toxic exposures than are lean children because of the content of their diet; higher consumption of fatty animal-based foods is correlated with higher levels of many POPs in human serum and milk.[180–182] Given the number of POPs that are candidate obesogens, reducing consumption of animal-based fatty foods is likely a sound anti-obesity life style choice both because of the nutritional benefit and the reduction of exposure to chemical contaminants.

## ACKNOWLEDGMENTS

The information in this document has been reviewed by the National Institute of Environmental Health Sciences and approved for publication. Approval does not signify that the contents necessarily reflect the views of the agency, nor does the mention of trade names or commercial products constitute endorsement or recommendation for use.

This research was funded by the Research Training Program in Environmental Pediatrics of the National Institutes of Health (ML: T32HD049311).

## DISCLOSURES

*Potential conflict of interest:* Nothing to report.

## REFERENCES

1. Wang Y, Lobstein T. Worldwide trends in childhood overweight and obesity. *Int J Pediatr Obes* 2006; 1(1): 11–25.

2. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA* Apr 5 2006; 295(13): 1549–1555.
3. Bolding J, Wratchford T, Perkins K, Ogershok P. Prevalence of obesity, acanthosis nigricans and hyperinsulinemia in an adolescent clinic. *W V Med J* May-Jun 2005; 101(3): 112–115.
4. Stewart ST, Cutler DM, Rosen AB. Forecasting the effects of obesity and smoking on U.S. life expectancy. *N Engl J Med* Dec 3 2009; 361(23): 2252–2260.
5. Carmichael AR. Obesity and prognosis of breast cancer. *Obes Rev* Nov 2006; 7(4): 333–340.
6. Shaw J. Epidemiology of childhood type 2 diabetes and obesity. *Pediatr Diabetes* Dec 2007; 8(Suppl 9): 7–15.
7. Cawley J, Meyerhoefer C. *The medical care costs of obesity: an instrumental variables approach*: National Bureau of Economic Research; 2010.
8. Newbold RR. Impact of environmental endocrine disrupting chemicals on the development of obesity. *Hormones (Athens)* Jul-Sep 2010; 9(3): 206–217.
9. Grun F, Blumberg B. Endocrine disrupters as obesogens. *Mol Cell Endocrinol* May 25 2009; 304(1-2): 19–29.
10. Roseboom T, de Rooij S, Painter R. The Dutch famine and its long-term consequences for adult health. *Early Hum Dev* Aug 2006; 82(8): 485–491.
11. Schack-Nielsen L, Michaelsen KF, Gamborg M, Mortensen EL, Sorensen TI. Gestational weight gain in relation to offspring body mass index and obesity from infancy through adulthood. *Int J Obes (Lond)* Jan 2010; 34(1): 67–74.
12. Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study: associations with maternal body mass index. *BJOG* Apr 2010; 117(5): 575–584.
13. Ng SF, Lin RC, Laybutt DR, Barres R, Owens JA, Morris MJ. Chronic high-fat diet in fathers programs beta-cell dysfunction in female rat offspring. *Nature* Oct 21 2010; 467(7318): 963–966.
14. Huang JS, Lee TA, Lu MC. Prenatal programming of childhood overweight and obesity. *Matern Child Health J* Sep 2007; 11(5): 461–473.
15. Hillier TA, Pedula KL, Schmidt MM, Mullen JA, Charles MA, Pettitt DJ. Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia. *Diabetes Care* Sep 2007; 30(9): 2287–2292.
16. Ong KK. Early determinants of obesity. *Endocr Dev* 2010; 19: 53–61.
17. Saenger P, Czernichow P, Hughes I, Reiter EO. Small for gestational age: short stature and beyond. *Endocr Rev* Apr 2007; 28(2): 219–251.
18. Weiderpass E, Braaten T, Magnusson C, et al. A prospective study of body size in different periods of life and risk of premenopausal breast cancer. *Cancer Epidemiol Biomarkers Prev* Jul 2004; 13(7): 1121–1127.
19. McMillen IC, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. *Physiol Rev* Apr 2005; 85(2): 571–633.
20. Birnbaum LS, Fenton SE. Cancer and developmental exposure to endocrine disruptors. *Environ Health Perspect* Apr 2003; 111(4): 389–394.
21. Salsberry PJ, Reagan PB. Taking the long view: the prenatal environment and early adolescent overweight. *Res Nurs Health* Jun 2007; 30(3): 297–307.
22. Montgomery SM, Ekbom A. Smoking during pregnancy and diabetes mellitus in a British longitudinal birth cohort. *BMJ* Jan 5 2002; 324(7328): 26–27.
23. Newbold RR, Padilla-Banks E, Snyder RJ, Phillips TM, Jefferson WN. Developmental exposure to endocrine disruptors and the obesity epidemic. *Reprod Toxicol* Jan 17 2007.
24. Hines EP, White SS, Stanko JP, Gibbs-Flournoy EA, Lau C, Fenton SE. Phenotypic dichotomy following developmental exposure to perfluorooctanoic acid (PFOA) in female CD-1 mice: Low doses induce elevated serum leptin and insulin, and overweight in mid-life. *Mol Cell Endocrinol* May 25 2009; 304(1–2): 97–105.
25. Huang RC, Mori TA, Burke V, et al. Synergy between adiposity, insulin resistance, metabolic risk factors, and inflammation in adolescents. *Diabetes Care* Apr 2009; 32(4): 695–701.
26. Spathopoulos D, Paraskakis E, Trypsianis G, et al. The effect of obesity on pulmonary lung function of school aged children in Greece. *Pediatr Pulmonol* Mar 2009; 44(3): 273–280.
27. Biro FM, Galvez MP, Greenspan LC, et al. Pubertal assessment method and baseline characteristics in a mixed longitudinal study of girls. *Pediatrics* Sep 2010; 126(3): e583–590.
28. Wolff MS, Britton JA, Teitelbaum SL, et al. Improving organochlorine biomarker models for cancer research. *Cancer Epidemiol Biomarkers Prev* Sep 2005; 14(9): 2224–2236.
29. Emond C, Birnbaum LS, DeVito MJ. Use of a physiologically based pharmacokinetic model for rats to study the influence of body fat mass and induction of CYP1A2 on the pharmacokinetics of TCDD. *Environ Health Perspect* Sep 2006; 114(9): 1394–1400.
30. Michalek JE, Tripathi RC. Pharmacokinetics of TCDD in veterans of Operation Ranch Hand: 15-year follow-up. *J Toxicol Environ Health A* Jul 23 1999; 57(6): 369–378.
31. Wolff MS, Zeleniuch-Jacquotte A, Dubin N, Toniolo P. Risk of breast cancer and organochlorine exposure. *Cancer Epidemiol Biomarkers Prev* Mar 2000; 9(3): 271–277.
32. Yoo JS, Norman JO, Busbee DL. Benzo[a]pyrene uptake by serum lipids: correlation with triglyceride concentration. *Proc Soc Exp Biol Med* Dec 1984; 177(3): 434–440.
33. Leighty EG, Fentiman AF, Jr., Thompson RM. Conjugation of fatty acids to DDT in the rat: possible mechanism for retention. *Toxicology* 1980; 15(2): 77–82.
34. Zaleski J, Kwei GY, Thurman RG, Kauffman FC. Suppression of benzo[a]pyrene metabolism by accumulation of triacylglycerols in rat hepatocytes: effect of high-fat and food-restricted diets. *Carcinogenesis* Nov 1991; 12(11): 2073–2079.
35. Van den Berg M, Birnbaum LS, Denison M, et al. The 2005 World Health Organization reevaluation of human and Mammalian toxic equivalency factors for dioxins and dioxin-like compounds. *Toxicol Sci* Oct 2006; 93(2): 223–241.
36. Patandin S, Koopman-Esseboom C, de Ridder MA, Weisglas-Kuperus N, Sauer PJ. Effects of environmental exposure to polychlorinated biphenyls and dioxins on birth size and growth in Dutch children. *Pediatr Res* Oct 1998; 44(4): 538–545.
37. Hunt LP, Ford A, Sabin MA, Crowne EC, Shield JP. Clinical measures of adiposity and percentage fat loss: which measure most accurately reflects fat loss and what should we aim for? *Arch Dis Child* May 2007; 92(5): 399–403.


DOI:10.1002/MSJ

38. Cole TJ, Faith MS, Pietrobelli A, Heo M. What is the best measure of adiposity change in growing children: BMI, BMI %, BMI z-score or BMI centile? *Eur J Clin Nutr* Mar 2005; 59(3): 419–425.
39. Karmaus W, Osuch JR, Eneli I, et al. Maternal levels of dichlorodiphenyl-dichloroethylene (DDE) may increase weight and body mass index in adult female offspring. *Occup Environ Med* Mar 2009; 66(3): 143–149.
40. Gladen BC, Ragan NB, Rogan WJ. Pubertal growth and development and prenatal and lactational exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene. *J Pediatr* Apr 2000; 136(4): 490–496.
41. Verhulst SL, Nelen V, Hond ED, et al. Intrauterine exposure to environmental pollutants and body mass index during the first 3 years of life. *Environ Health Perspect* Jan 2009; 117(1): 122–126.
42. Dhooge W, Den Hond E, Koppen G, et al. Internal exposure to pollutants and body size in Flemish adolescents and adults: associations and dose-response relationships. *Environ Int* May 2010; 36(4): 330–337.
43. Uemura H, Arisawa K, Hiyoshi M, et al. Prevalence of metabolic syndrome associated with body burden levels of dioxin and related compounds among Japan's general population. *Environ Health Perspect* Apr 2009; 117(4): 568–573.
44. Lee DH, Lee IK, Porta M, Steffes M, Jacobs DR, Jr. Relationship between serum concentrations of persistent organic pollutants and the prevalence of metabolic syndrome among non-diabetic adults: results from the National Health and Nutrition Examination Survey 1999–2002. *Diabetologia* Sep 2007; 50(9): 1841–1851.
45. Ha MH, Lee DH, Jacobs DR. Association between serum concentrations of persistent organic pollutants and self-reported cardiovascular disease prevalence: results from the National Health and Nutrition Examination Survey, 1999–2002. *Environ Health Perspect* Aug 2007; 115(8): 1204–1209.
46. Chang JW, Chen HL, Su HJ, Liao PC, Guo HR, Lee CC. Dioxin exposure and insulin resistance in Taiwanese living near a highly contaminated area. *Epidemiology* Jan 2010; 21(1): 56–61.
47. Lilienthal H, Hack A, Roth-Harer A, Grande SW, Talsness CE. Effects of developmental exposure to 2,2 ,4,4 ,5-pentabromodiphenyl ether (PBDE-99) on sex steroids, sexual development, and sexually dimorphic behavior in rats. *Environ Health Perspect* Feb 2006; 114(2): 194–201.
48. La Merrill M, Baston DS, Denison MS, Birnbaum LS, Pomp D, Threadgill DW. Mouse breast cancer model-dependent changes in metabolic syndrome-associated phenotypes caused by maternal dioxin exposure and dietary fat. *Am J Physiol Endocrinol Metab* 2009; 296(1): E203–210.
49. La Merrill M, Kuruvilla BS, Pomp D, Birnbaum LS, Threadgill DW. Dietary fat alters body composition, mammary development and P450 induction following maternal TCDD exposure in DBA/2J mice with low responsive aryl hydrocarbon receptors. *Environ Health Perspect* 2009; 117(9): 1414–1419.
50. Vogel CF, Matsumura F. Interaction of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) with induced adipocyte differentiation in mouse embryonic fibroblasts (MEFs) involves tyrosine kinase c-Src. *Biochem Pharmacol* Oct 1 2003; 66(7): 1231–1244.
51. Phillips M, Enan E, Liu PC, Matsumura F. Inhibition of 3T3-L1 adipose differentiation by 2,3,7,8-tetrachlorodibenzo-p-dioxin. *J Cell Sci* Jan 1995; 108(Pt 1): 395–402.
52. Arsenescu V, Arsenescu RI, King V, Swanson H, Cassis LA. Polychlorinated biphenyl-77 induces adipocyte differentiation and proinflammatory adipokines and promotes obesity and atherosclerosis. *Environ Health Perspect* Jun 2008; 116(6): 761–768.
53. Spalding KL, Arner E, Westermark PO, et al. Dynamics of fat cell turnover in humans. *Nature* Jun 5 2008; 453(7196): 783–787.
54. Arner P, Spalding KL. Fat cell turnover in humans. *Biochem Biophys Res Commun* May 21 2010; 396(1): 101–104.
55. Kopec AK, Burgoon LD, Ibrahim-Aibo D, et al. Automated dose-response analysis and comparative toxicogenomic evaluation of the hepatic effects elicited by TCDD, TCDF, and PCB126 in C57BL/6 mice. *Toxicol Sci* Nov 2010; 118(1): 286–297.
56. Branchi I, Alleva E, Costa LG. Effects of perinatal exposure to a polybrominated diphenyl ether (PBDE 99) on mouse neurobehavioural development. *Neurotoxicology* Sep 2002; 23(3): 375–384.
57. DeLong GT, Rice CD. Tributyltin potentiates 3,3',4,4',5-pentachlorobiphenyl-induced cytochrome P-4501A-related activity. *J Toxicol Environ Health* Jun 6 1997; 51(2): 131–148.
58. Gladen BC, Klebanoff MA, Hediger ML, et al. Prenatal DDT exposure in relation to anthropometric and pubertal measures in adolescent males. *Environ Health Perspect* Dec 2004; 112(17): 1761–1767.
59. Mendez MA, Garcia-Esteban R, Guxens M, et al. Prenatal Organochlorine Compound Exposure, Rapid Weight Gain and Overweight in Infancy. *Environ Health Perspect* Oct 5 2010.
60. Smink A, Ribas-Fito N, Garcia R, et al. Exposure to hexachlorobenzene during pregnancy increases the risk of overweight in children aged 6 years. *Acta Paediatr* Oct 2008; 97(10): 1465–1469.
61. Lee DH, Lee IK, Jin SH, Steffes M, Jacobs DR, Jr. Association between serum concentrations of persistent organic pollutants and insulin resistance among nondiabetic adults: results from the National Health and Nutrition Examination Survey 1999–2002. *Diabetes Care* Mar 2007; 30(3): 622–628.
62. Lee SA, Dai Q, Zheng W, et al. Association of serum concentration of organochlorine pesticides with dietary intake and other lifestyle factors among urban Chinese women. *Environ Int* Feb 2007; 33(2): 157–163.
63. Perry MJ, Ouyang F, Korrick S, et al. Body mass index and serum 1,1,1-trichloro-2,2-bis(p-chlorophenyl) ethane in nulliparous Chinese women. *Cancer Epidemiol Biomarkers Prev* Oct 2005; 14(10): 2433–2438.
64. Arnold DL, Moodie CA, Charbonneau SM, et al. Long-term toxicity of hexachlorobenzene in the rat and the effect of dietary vitamin A. *Food Chem Toxicol* Sep 1985; 23(9): 779–793.
65. Randi AS, Sancovich HA, Ferramola de Sancovich AM, et al. Effect of in vivo administered hexachlorobenzene on epidermal growth factor receptor levels, protein tyrosine kinase activity, and phosphotyrosine content in rat liver. *Biochem Pharmacol* May 1 2003; 65(9): 1495–1506.
66. Alvarez L, Randi A, Alvarez P, et al. Reproductive effects of hexachlorobenzene in female rats. *J Appl Toxicol* Jan-Feb 2000; 20(1): 81–87.
67. Palanza P, Parmigiani S, vom Saal FS. Effects of prenatal exposure to low doses of diethylstilbestrol,

DOI:10.1002/MSJ

o,p'DDT, and methoxychlor on postnatal growth and neurobehavioral development in male and female mice. *Horm Behav* Sep 2001; 40(2): 252–265.
68. Makita Y, Omura M, Tanaka A, Kiyohara C. Effects of concurrent exposure to tributyltin and 1,1-dichloro-2,2 bis (p-chlorophenyl) ethylene (p,p'-DDE) on immature male Wistar rats. *Basic Clin Pharmacol Toxicol* Dec 2005; 97(6): 364–368.
69. Makita Y, Tanaka A, Omura M, Ogata R. Effects of simultaneous administration of tributyltin (TBT) and p,p(')-DDE on female offspring of Wistar rats. *J Toxicol Environ Health A* Dec 26 2003; 66(24): 2337–2347.
70. Bell JU, Hansell MM, Ecobichon DJ. The influence of DDT on the ontogenesis of drug-metabolizing enzymes in the perinatal rat. *Toxicol Appl Pharmacol* Jan 1976; 35(1): 165–177.
71. Ozcan U, Cao Q, Yilmaz E, et al. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. *Science* Oct 15 2004; 306(5695): 457–461.
72. Gregor MF, Yang L, Fabbrini E, et al. Endoplasmic reticulum stress is reduced in tissues of obese subjects after weight loss. *Diabetes* Mar 2009; 58(3): 693–700.
73. Sanyal S, Agarwal N, Dudeja PK, Mahmood A, Subrahmanyam D. Effect of a single oral dose of DDT on lipid metabolism in protein-calorie malnourished monkeys. *Indian J Biochem Biophys* Apr 1982; 19(2): 111–114.
74. Sanyal S, Agarwal N, Subrahmanyam D. Effect of acute sublethal and chronic administration of DDT (chlorophenotane) on brain lipid metabolism of rhesus monkeys. *Toxicol Lett* Nov 1986; 34(1): 47–54.
75. Van den Heuvela F. Decomposition analysis of differential dose volume histograms. *Med Phys* Feb 2006; 33(2): 297–307.
76. Rosen MB, Lee JS, Ren H, et al. Toxicogenomic dissection of the perfluorooctanoic acid transcript profile in mouse liver: evidence for the involvement of nuclear receptors PPAR alpha and CAR. *Toxicol Sci* May 2008; 103(1): 46–56.
77. Feige JN, Gerber A, Casals-Casas C, et al. The pollutant diethylhexyl phthalate regulates hepatic energy metabolism via species-specific PPARalpha-dependent mechanisms. *Environ Health Perspect* Feb 2010; 118(2): 234–241.
78. Nelson JW, Hatch EE, Webster TF. Exposure to polyfluoroalkyl chemicals and cholesterol, body weight, and insulin resistance in the general U.S. population. *Environ Health Perspect* Feb 2010; 118(2): 197–202.
79. Lin CY, Chen PC, Lin YC, Lin LY. Association among serum perfluoroalkyl chemicals, glucose homeostasis, and metabolic syndrome in adolescents and adults. *Diabetes Care* Apr 2009; 32(4): 702–707.
80. Melzer D, Rice N, Depledge MH, Henley WE, Galloway TS. Association between serum perfluorooctanoic acid (PFOA) and thyroid disease in the U.S. National Health and Nutrition Examination Survey. *Environ Health Perspect* May 2010; 118(5): 686–692.
81. Fei C, McLaughlin JK, Tarone RE, Olsen J. Perfluorinated chemicals and fetal growth: a study within the Danish National Birth Cohort. *Environ Health Perspect* Nov 2007; 115(11): 1677–1682.
82. Apelberg BJ, Witter FR, Herbstman JB, et al. Cord serum concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) in relation to weight and size at birth. *Environ Health Perspect* Nov 2007; 115(11): 1670–1676.
83. Yang C, Tan YS, Harkema JR, Haslam SZ. Differential effects of peripubertal exposure to perfluorooctanoic acid on mammary gland development in C57Bl/6 and Balb/c mouse strains. *Reprod Toxicol* Jun 2009; 27(3-4): 299–306.
84. Wolf CJ, Fenton SE, Schmid JE, et al. Developmental toxicity of perfluorooctanoic acid in the CD-1 mouse after cross-foster and restricted gestational exposures. *Toxicol Sci* Feb 2007; 95(2): 462–473.
85. Perez-Maldonado IN, Ramirez-Jimenez Mdel R, Martinez-Arevalo LP, et al. Exposure assessment of polybrominated diphenyl ethers (PBDEs) in Mexican children. *Chemosphere* May 2009; 75(9): 1215–1220.
86. Athanasiadou M, Cuadra SN, Marsh G, Bergman A, Jakobsson K. Polybrominated diphenyl ethers (PBDEs) and bioaccumulative hydroxylated PBDE metabolites in young humans from Managua, Nicaragua. *Environ Health Perspect* Mar 2008; 116(3): 400–408.
87. Fischer D, Hooper K, Athanasiadou M, Athanassiadis I, Bergman A. Children show highest levels of polybrominated diphenyl ethers in a California family of four: a case study. *Environ Health Perspect* Oct 2006; 114(10): 1581–1584.
88. Toms LM, Sjodin A, Harden F, et al. Serum polybrominated diphenyl ether (PBDE) levels are higher in children (2-5 years of age) than in infants and adults. *Environ Health Perspect* Sep 2009; 117(9): 1461–1465.
89. Toms LM, Harden F, Paepke O, Hobson P, Ryan JJ, Mueller JF. Higher accumulation of polybrominated diphenyl ethers in infants than in adults. *Environ Sci Technol* Oct 1 2008; 42(19): 7510–7515.
90. DiGangi J, Blum A, Bergman A, et al. San Antonio statement on brominated and chlorinated flame retardants. *Environ Health Perspect* 2010; 118: A516–A518.
91. Frederiksen M, Thomsen M, Vorkamp K, Knudsen LE. Patterns and concentration levels of polybrominated diphenyl ethers (PBDEs) in placental tissue of women in Denmark. *Chemosphere* Sep 2009; 76(11): 1464–1469.
92. Daniels JL, Pan IJ, Jones R, et al. Individual Characteristics Associated with PBDE Levels in U.S. Human Milk Samples. *Environ Health Perspect* Jan;118(1): 155–160.
93. Gee JR, Moser VC. Acute postnatal exposure to brominated diphenylether 47 delays neuromotor ontogeny and alters motor activity in mice. *Neurotoxicol Teratol* Mar-Apr 2008; 30(2): 79–87.
94. Fernie KJ, Laird Shutt J, Ritchie IJ, Letcher RJ, Drouillard K, Bird DM. Changes in the growth, but not the survival, of American kestrels (Falco sparverius) exposed to environmentally relevant polybrominated diphenyl ethers. *J Toxicol Environ Health A* Aug 2006; 69(16): 1541–1554.
95. Suvorov A, Battista MC, Takser L. Perinatal exposure to low-dose 2,2',4,4'-tetrabromodiphenyl ether affects growth in rat offspring: what is the role of IGF-1? *Toxicology* Jun 16 2009; 260(1-3): 126–131.
96. Hoppe AA, Carey GB. Polybrominated diphenyl ethers as endocrine disruptors of adipocyte metabolism. *Obesity (Silver Spring)* Dec 2007; 15(12): 2942–2950.
97. Key PB, Chung KW, Hoguet J, Shaddrix B, Fulton MH. Toxicity and physiological effects of brominated flame retardant PBDE-47 on two life stages of grass shrimp, Palaemonetes pugio. *Sci Total Environ* Jul 25 2008; 399(1-3): 28–32.
98. Hatch EE, Nelson JW, Qureshi MM, et al. Association of urinary phthalate metabolite concentrations with

body mass index and waist circumference: a cross-sectional study of NHANES data, 1999–2002. *Environ Health* 2008; 7: 27.
99. Wolff MS, Teitelbaum SL, Windham G, et al. Pilot study of urinary biomarkers of phytoestrogens, phthalates, and phenols in girls. *Environ Health Perspect* Jan 2007; 115(1): 116–121.
100. Stahlhut RW, van Wijngaarden E, Dye TD, Cook S, Swan SH. Concentrations of urinary phthalate metabolites are associated with increased waist circumference and insulin resistance in adult U.S. males. *Environ Health Perspect* Jun 2007; 115(6): 876–882.
101. Feige JN, Gelman L, Rossi D, et al. The endocrine disruptor monoethyl-hexyl-phthalate is a selective peroxisome proliferator-activated receptor gamma modulator that promotes adipogenesis. *J Biol Chem* Jun 29 2007; 282(26): 19152–19166.
102. Hurst CH, Waxman DJ. Activation of PPARalpha and PPARgamma by environmental phthalate monoesters. *Toxicol Sci* Aug 2003; 74(2): 297–308.
103. Sargis RM, Johnson DN, Choudhury RA, Brady MJ. Environmental endocrine disruptors promote adipogenesis in the 3T3-L1 cell line through glucocorticoid receptor activation. *Obesity (Silver Spring)* Jul 2010; 18(7): 1283–1288.
104. Poon R, Lecavalier P, Mueller R, Valli VE, Procter BG, Chu I. Subchronic oral toxicity of di-n-octyl phthalate and di(2-Ethylhexyl) phthalate in the rat. *Food Chem Toxicol* Feb 1997; 35(2): 225–239.
105. Stein MS, Caasi PI, Nair PP. Influence of dietary fat and di-2-ethylhexyl phthalate on tissue lipids in rats. *J Nutr* Feb 1974; 104(2): 187–191.
106. Wang YF, Chao HR, Wu CH, Tseng CH, Kuo YT, Tsou TC. A recombinant peroxisome proliferator response element-driven luciferase assay for evaluation of potential environmental obesogens. *Biotechnol Lett* Jul 28 2010.
107. Bishop-Bailey HD, Hla T, Warner TD. Bisphenol A diglycidyl ether (BADGE) is a PPAR gamma agonist in an ECV304 cell line. *Brit J Pharm* 2000; 131: 651–654.
108. Lang IA, Galloway TS, Scarlett A, et al. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. *JAMA* Sep 17 2008; 300(11): 1303–1310.
109. Richter CA, Birnbaum LS, Farabollini F, et al. In vivo effects of bisphenol A in laboratory rodent studies. *Reprod Toxicol* Aug-Sep 2007; 24(2): 199–224.
110. Alonso-Magdalena P, Vieira E, Soriano S, et al. Bisphenol A Exposure during Pregnancy Disrupts Glucose Homeostasis in Mothers and Adult Male Offspring. *Environ Health Perspect* Sep 2010; 118(9): 1243–1250.
111. Ryan KK, Haller AM, Sorrell JE, Woods SC, Jandacek RJ, Seeley RJ. Perinatal exposure to bisphenol-a and the development of metabolic syndrome in CD-1 mice. *Endocrinology* Jun 2010; 151(6): 2603–2612.
112. Stump DG, Beck MJ, Radovsky A, et al. Developmental neurotoxicity study of dietary bisphenol A in Sprague-Dawley rats. *Toxicol Sci* May 2010; 115(1): 167–182.
113. Nakamura D, Yanagiba Y, Duan Z, et al. Bisphenol A may cause testosterone reduction by adversely affecting both testis and pituitary systems similar to estradiol. *Toxicol Lett* Apr 15 2010; 194(1-2): 16–25.
114. Takai Y, Tsutsumi O, Ikezuki Y, et al. Estrogen receptor-mediated effects of a xenoestrogen, bisphenol A, on preimplantation mouse embryos. *Biochem Biophys Res Commun* Apr 21 2000; 270(3): 918–921.
115. Takai Y, Tsutsumi O, Ikezuki Y, et al. Preimplantation exposure to bisphenol A advances postnatal development. *Reprod Toxicol* Jan-Feb 2001; 15(1): 71–74.
116. Masuno H, Iwanami J, Kidani T, Sakayama K, Honda K. Bisphenol a accelerates terminal differentiation of 3T3-L1 cells into adipocytes through the phosphatidylinositol 3-kinase pathway. *Toxicol Sci* Apr 2005; 84(2): 319–327.
117. Masuno H, Kidani T, Sekiya K, et al. Bisphenol A in combination with insulin can accelerate the conversion of 3T3-L1 fibroblasts to adipocytes. *J Lipid Res* May 2002; 43(5): 676–684.
118. Kanayama T, Kobayashi N, Mamiya S, Nakanishi T, Nishikawa J. Organotin compounds promote adipocyte differentiation as agonists of the peroxisome proliferator-activated receptor gamma/retinoid X receptor pathway. *Mol Pharmacol* Mar 2005; 67(3): 766–774.
119. Grun F, Watanabe H, Zamanian Z, et al. Endocrine-disrupting organotin compounds are potent inducers of adipogenesis in vertebrates. *Mol Endocrinol* Sep 2006; 20(9): 2141–2155.
120. Grote K, Hobler C, Andrade AJ, et al. Effects of in utero and lactational exposure to triphenyltin chloride on pregnancy outcome and postnatal development in rat offspring. *Toxicology* Sep 5 2007; 238(2-3): 177–185.
121. Delgado IF, Viana VG, Sarpa M, Paumgartten FJ. Postnatal development and resistance to Plasmodium yoelii infection of mice prenatally exposed to triphenyltin hydroxide. *Environ Toxicol* Dec 2009; 24(6): 629–635.
122. Asakawa H, Tsunoda M, Kaido T, et al. Enhanced inhibitory effects of TBT chloride on the development of F1 rats. *Arch Environ Contam Toxicol* May 2010; 58(4): 1065–1073.
123. Tsunoda M, Aizawa Y, Konno N, Kimura K, Sugita-Konishi Y. Subacute administration of tributyltin chloride modulates neurotransmitters and their metabolites in discrete brain regions of maternal mice and their F1 offspring. *Toxicol Ind Health* Feb 2006; 22(1): 15–25.
124. Kirchner S, Kieu T, Chow C, Casey S, Blumberg B. Prenatal exposure to the environmental obesogen tributyltin predisposes multipotent stem cells to become adipocytes. *Mol Endocrinol* Mar 2010; 24(3): 526–539.
125. Si J, Wu X, Wan C, et al. Peripubertal exposure to low doses of tributyltin chloride affects the homeostasis of serum T, E2, LH, and body weight of male mice. *Environ Toxicol* Jan 5 2010.
126. Zuo Z, Chen S, Wu T, et al. Tributyltin causes obesity and hepatic steatosis in male mice. *Environ Toxicol* Sep 16 2009.
127. Cooke GM, Tryphonas H, Pulido O, Caldwell D, Bondy GS, Forsyth D. Oral (gavage), in utero and postnatal exposure of Sprague-Dawley rats to low doses of tributyltin chloride. Part 1: Toxicology, histopathology and clinical chemistry. *Food Chem Toxicol* Feb 2004; 42(2): 211–220.
128. Inadera H, Shimomura A. Environmental chemical tributyltin augments adipocyte differentiation. *Toxicol Lett* Dec 15 2005; 159(3): 226–234.
129. Kim R, Hu H, Rotnitzky A, Bellinger D, Needleman H. A longitudinal study of chronic lead exposure and physical growth in Boston children. *Environ Health Perspect* Oct 1995; 103(10): 952–957.
130. Hu H, Rabinowitz M, Smith D. Bone lead as a biological marker in epidemiologic studies of

DOI:10.1002/MSJ

chronic toxicity: conceptual paradigms. *Environ Health Perspect* Jan 1998; 106(1): 1–8.
131. Huzior-Balajewicz A, Pietrzyk JJ, Schlegel-Zawadzka M, Piatkowska E, Zachwieja Z. The influence of lead and cadmium environmental pollution on anthropometric health factors in children. *Przegl Lek* 2001; 58(4): 315–324.
132. Ronco AM, Gutierrez Y, Gras N, Munoz L, Salazar G, Llanos MN. Lead and arsenic levels in women with different body mass composition. *Biol Trace Elem Res* Sep 2010; 136(3): 269–278.
133. Park SK, Schwartz J, Weisskopf M, et al. Low-level lead exposure, metabolic syndrome, and heart rate variability: the VA Normative Aging Study. *Environ Health Perspect* Nov 2006; 114(11): 1718–1724.
134. Leasure JL, Giddabasappa A, Chaney S, et al. Low-level human equivalent gestational lead exposure produces sex-specific motor and coordination abnormalities and late-onset obesity in year-old mice. *Environ Health Perspect* Mar 2008; 116(3): 355–361.
135. von Kries R, Bolte G, Baghi L, Toschke AM. Parental smoking and childhood obesity--is maternal smoking in pregnancy the critical exposure? *Int J Epidemiol* Feb 2008; 37(1): 210–216.
136. Toschke AM, Montgomery SM, Pfeiffer U, von Kries R. Early intrauterine exposure to tobacco-inhaled products and obesity. *Am J Epidemiol* Dec 1 2003; 158(11): 1068–1074.
137. Syme C, Abrahamowicz M, Mahboubi A, et al. Prenatal exposure to maternal cigarette smoking and accumulation of intra-abdominal fat during adolescence. *Obesity (Silver Spring)* May 2010; 18(5): 1021–1025.
138. Ng SP, Conklin DJ, Bhatnagar A, Bolanowski DD, Lyon J, Zelikoff JT. Prenatal exposure to cigarette smoke induces diet- and sex-dependent dyslipidemia and weight gain in adult murine offspring. *Environ Health Perspect* Jul 2009; 117(7): 1042–1048.
139. Somm E, Schwitzgebel VM, Vauthay DM, et al. Prenatal nicotine exposure alters early pancreatic islet and adipose tissue development with consequences on the control of body weight and glucose metabolism later in life. *Endocrinology* Dec 2008; 149(12): 6289–6299.
140. Irigaray P, Ogier V, Jacquenet S, et al. Benzo[a]pyrene impairs beta-adrenergic stimulation of adipose tissue lipolysis and causes weight gain in mice. A novel molecular mechanism of toxicity for a common food pollutant. *FEBS J* Apr 2006; 273(7): 1362–1372.
141. Tsukue N, Kato A, Ito T, Sugiyama G, Nakajima T. Acute effects of diesel emission from the urea selective catalytic reduction engine system on male rats. *Inhal Toxicol* Mar 2010; 22(4): 309–320.
142. Shimada T, Hiramatsu N, Hayakawa K, et al. Dual suppression of adipogenesis by cigarette smoke through activation of the aryl hydrocarbon receptor and induction of endoplasmic reticulum stress. *Am J Physiol Endocrinol Metab* Apr 2009; 296(4): E721–730.
143. Newbold RR, Padilla-Banks E, Jefferson WN. Environmental estrogens and obesity. *Mol Cell Endocrinol* May 25 2009; 304(1-2): 84–89.
144. Newbold RR, Jefferson WN, Padilla-Banks E, Haseman J. Developmental exposure to diethylstilbestrol (DES) alters uterine response to estrogens in prepubescent mice: low versus high dose effects. *Reprod Toxicol* May 2004; 18(3): 399–406.
145. Cagen SZ, Waechter JM, Jr., Dimond SS, et al. Normal reproductive organ development in CF-1 mice following prenatal exposure to bisphenol A. *Toxicol Sci* Jul 1999; 50(1): 36–44.
146. Honma S, Suzuki A, Buchanan DL, Katsu Y, Watanabe H, Iguchi T. Low dose effect of in utero exposure to bisphenol A and diethylstilbestrol on female mouse reproduction. *Reprod Toxicol* Mar-Apr 2002; 16(2): 117–122.
147. Ashby J, Tinwell H, Haseman J. Lack of effects for low dose levels of bisphenol A and diethylstilbestrol on the prostate gland of CF1 mice exposed in utero. *Regul Toxicol Pharmacol* Oct 1999; 30(2 Pt 1): 156–166.
148. Gupta C. Reproductive malformation of the male offspring following maternal exposure to estrogenic chemicals. *Proc Soc Exp Biol Med* Jun 2000; 224(2): 61–68.
149. Nikaido Y, Yoshizawa K, Danbara N, et al. Effects of maternal xenoestrogen exposure on development of the reproductive tract and mammary gland in female CD-1 mouse offspring. *Reprod Toxicol* Aug-Sep 2004; 18(6): 803–811.
150. Miyawaki J, Sakayama K, Kato H, Yamamoto H, Masuno H. Perinatal and postnatal exposure to bisphenol a increases adipose tissue mass and serum cholesterol level in mice. *J Atheroscler Thromb* Oct 2007; 14(5): 245–252.
151. Olfson M, Blanco C, Liu L, Moreno C, Laje G. National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. *Arch Gen Psychiatry* Jun 2006; 63(6): 679–685.
152. Correll CU. Assessing and maximizing the safety and tolerability of antipsychotics used in the treatment of children and adolescents. *J Clin Psychiatry* 2008; 69(Suppl 4): 26–36.
153. Walter G, DeLaroche A, Soh N, et al. Side effects of second-generation antipsychotics: the experiences, views and monitoring practices of Australian child psychiatrists. *Australas Psychiatry* Aug 2008; 16(4): 253–262.
154. Ratzoni G, Gothelf D, Brand-Gothelf A, et al. Weight gain associated with olanzapine and risperidone in adolescent patients: a comparative prospective study. *J Am Acad Child Adolesc Psychiatry* Mar 2002; 41(3): 337–343.
155. McIntyre RS, Jerrell JM. Metabolic and cardiovascular adverse events associated with antipsychotic treatment in children and adolescents. *Arch Pediatr Adolesc Med* Oct 2008; 162(10): 929–935.
156. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA* Oct 28 2009; 302(16): 1765–1773.
157. Mishra AC, Mohanty B. Effect of lactational exposure of olanzapine on body weight of mice: a comparative study on neonates of both the sexes during post-natal development. *J Psychopharmacol* Jul 2010; 24(7): 1089–1096.
158. Fell MJ, Neill JC, Rao C, Marshall KM. Effects of sub-chronic antipsychotic drug treatment on body weight and reproductive function in juvenile female rats. *Psychopharmacology (Berl)* Nov 2005; 182(4): 499–507.
159. Maayan L, Vakhrusheva J, Correll CU. Effectiveness of medications used to attenuate antipsychotic-related weight gain and metabolic abnormalities: a systematic review and meta-analysis. *Neuropsychopharmacology* Jun 2010; 35(7): 1520–1530.
160. Larsen TM, Toubro S, Astrup A. PPARgamma agonists in the treatment of type II diabetes: is increased fatness commensurate with long-term efficacy? *Int J Obes Relat Metab Disord* Feb 2003; 27(2): 147–161.

DOI:10.1002/MSJ

161. Musso G, Gambino R, Cassader M, Pagano G. A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease. *Hepatology* Jul 2010; 52(1): 79–104.
162. Rubenstrunk A, Hanf R, Hum DW, Fruchart JC, Staels B. Safety issues and prospects for future generations of PPAR modulators. *Biochim Biophys Acta* Aug 2007; 1771(8): 1065–1081.
163. Zdravkovic V, Hamilton JK, Daneman D, Cummings EA. Pioglitazone as adjunctive therapy in adolescents with type 1 diabetes. *J Pediatr* Dec 2006; 149(6): 845–849.
164. Stone ML, Walker JL, Chisholm D, et al. The addition of rosiglitazone to insulin in adolescents with type 1 diabetes and poor glycaemic control: a randomized-controlled trial. *Pediatr Diabetes* Jul 28 2008; 9(4 Pt 1): 326–334.
165. Szocs Z, Brunmair B, Stadlbauer K, et al. Age-dependent development of metabolic derangement and effects of intervention with pioglitazone in Zucker diabetic fatty rats. *J Pharmacol Exp Ther* Jul 2008; 326(1): 323–329.
166. Garg M, Thamotharan M, Pan G, Lee PW, Devaskar SU. Early exposure of the pregestational intrauterine and postnatal growth-restricted female offspring to a peroxisome proliferator-activated receptor-{gamma} agonist. *Am J Physiol Endocrinol Metab* Mar 2010; 298(3): E489–498.
167. Sato K, Matsushita K, Matsubara Y, Kamada T, Akiba Y. Adipose tissue fat accumulation is reduced by a single intraperitoneal injection of peroxisome proliferator-activated receptor gamma agonist when given to newly hatched chicks. *Poult Sci* Nov 2008; 87(11): 2281–2286.
168. Sevillano J, Lopez-Perez IC, Herrera E, Del Pilar Ramos M, Bocos C. Englitazone administration to late pregnant rats produces delayed body growth and insulin resistance in their fetuses and neonates. *Biochem J* Aug 1 2005; 389(Pt 3): 913–918.
169. Kroeze WK, Hufeisen SJ, Popadak BA, et al. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmacology* Mar 2003; 28(3): 519–526.
170. Templeman LA, Reynolds GP, Arranz B, San L. Polymorphisms of the 5-HT2C receptor and leptin genes are associated with antipsychotic drug-induced weight gain in Caucasian subjects with a first-episode psychosis. *Pharmacogenet Genomics* Apr 2005; 15(4): 195–200.
171. Ellinger LK, Ipema HJ, Stachnik JM. Efficacy of metformin and topiramate in prevention and treatment of second-generation antipsychotic-induced weight gain. *Ann Pharmacother* Apr 2010; 44(4): 668–679.
172. Eskenazi B, Chevrier J, Rosas LG, et al. The Pine River statement: human health consequences of DDT use. *Environ Health Perspect* Sep 2009; 117(9): 1359–1367.
173. La Merrill M, Harper R, Birnbaum LS, Cardiff RD, Threadgill DW. Maternal dioxin exposure combined with a diet high in fat increases mammary cancer incidence in mice. *Environ Health Perspect* May 2010; 118(5): 596–601.
174. Fujiyoshi PT, Michalek JE, Matsumura F. Molecular epidemiologic evidence for diabetogenic effects of dioxin exposure in U.S. Air force veterans of the Vietnam war. *Environ Health Perspect* Nov 2006; 114(11): 1677–1683.
175. Lee DH, Steffes MW, Jacobs DR, Jr. Can persistent organic pollutants explain the association between serum gamma-glutamyltransferase and type 2 diabetes? *Diabetologia* Mar 2008; 51(3): 402–407.
176. Lassiter TL, Ryde IT, Mackillop EA, et al. Exposure of neonatal rats to parathion elicits sex-selective reprogramming of metabolism and alters the response to a high-fat diet in adulthood. *Environ Health Perspect* Nov 2008; 116(11): 1456–1462.
177. Tuomisto JT, Pohjanvirta R, Unkila M, Tuomisto J. TCDD-induced anorexia and wasting syndrome in rats: effects of diet-induced obesity and nutrition. *Pharmacol Biochem Behav* Apr 1999; 62(4): 735–742.
178. Shi H, Seeley RJ, Clegg DJ. Sexual differences in the control of energy homeostasis. *Front Neuroendocrinol* Aug 2009; 30(3): 396–404.
179. Marti-Cid R, Bocio A, Llobet JM, Domingo JL. Intake of chemical contaminants through fish and seafood consumption by children of Catalonia, Spain: health risks. *Food Chem Toxicol* Oct 2007; 45(10): 1968–1974.
180. LaKind JS, Amina Wilkins A, Berlin CM, Jr. Environmental chemicals in human milk: a review of levels, infant exposures and health, and guidance for future research. *Toxicol Appl Pharmacol* Jul 15 2004; 198(2): 184–208.
181. Goldman LR, Harnly M, Flattery J, Patterson DGJ, Needham LL. Serum polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans among people eating contaminated home-produced eggs and beef. *Environ Health Perspect* 2000; 108 13–19.
182. Dewailly E, Ryan JJ, Laliberte C, et al. Exposure of remote maritime populations to coplanar PCBs. *Environ Health Perspect* Jan 1994; 102(Suppl 1): 205–209.
183. Kabuto H, Amakawa M, Shishibori T. Exposure to bisphenol A during embryonic/fetal life and infancy increases oxidative injury and causes underdevelopment of the brain and testis in mice. *Life Sci* Apr 30 2004; 74(24): 2931–2940.
184. Ryan BC, Vandenbergh JG. Developmental exposure to environmental estrogens alters anxiety and spatial memory in female mice. *Horm Behav* Jun 2006; 50(1): 85–93.
185. Markey CM, Coombs MA, Sonnenschein C, Soto AM. Mammalian development in a changing environment: exposure to endocrine disruptors reveals the developmental plasticity of steroid-hormone target organs. *Evol Dev* Jan-Feb 2003; 5(1): 67–75.
186. Howdeshell KL, Hotchkiss AK, Thayer KA, Vandenbergh JG, vom Saal FS. Exposure to bisphenol A advances puberty. *Nature* Oct 21 1999; 401(6755): 763–764.
187. Akingbemi BT, Sottas CM, Koulova AI, Klinefelter GR, Hardy MP. Inhibition of testicular steroidogenesis by the xenoestrogen bisphenol A is associated with reduced pituitary luteinizing hormone secretion and decreased steroidogenic enzyme gene expression in rat Leydig cells. *Endocrinology* Feb 2004; 145(2): 592–603.
188. Rubin BS, Murray MK, Damassa DA, King JC, Soto AM. Perinatal exposure to low doses of bisphenol A affects body weight, patterns of estrous cyclicity, and plasma LH levels. *Environ Health Perspect* Jul 2001; 109(7): 675–680.
189. Ishido M, Masuo Y, Kunimoto M, Oka S, Morita M. Bisphenol A causes hyperactivity in the rat concomitantly with impairment of tyrosine hydroxylase immunoreactivity. *J Neurosci Res* May 1 2004; 76(3): 423–433.

DOI:10.1002/MSJ